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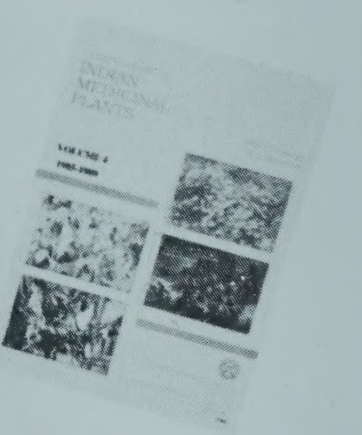
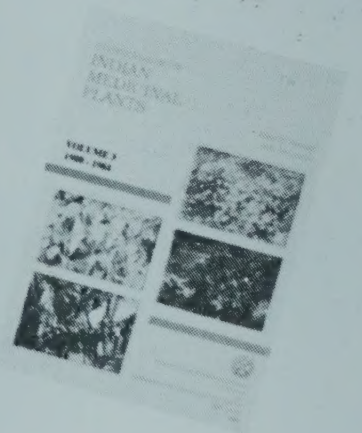
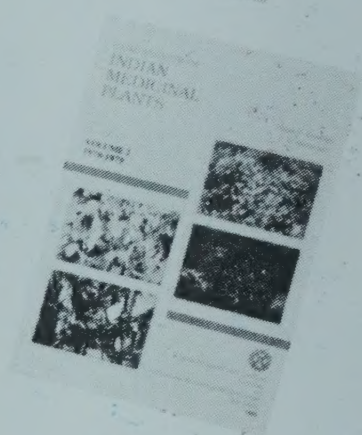
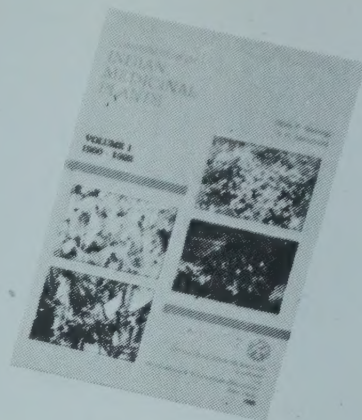
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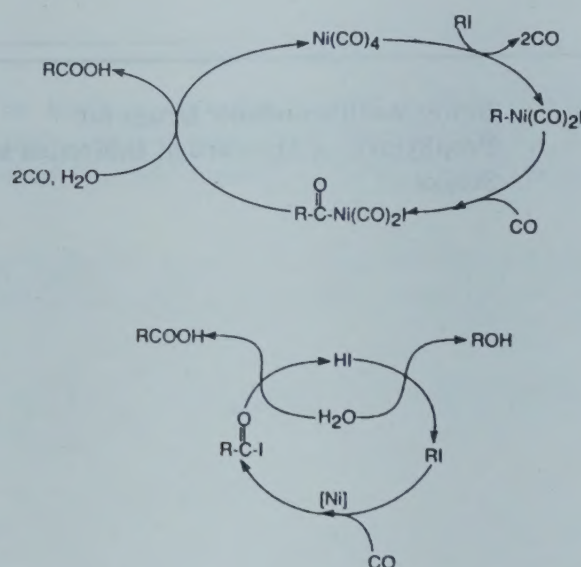
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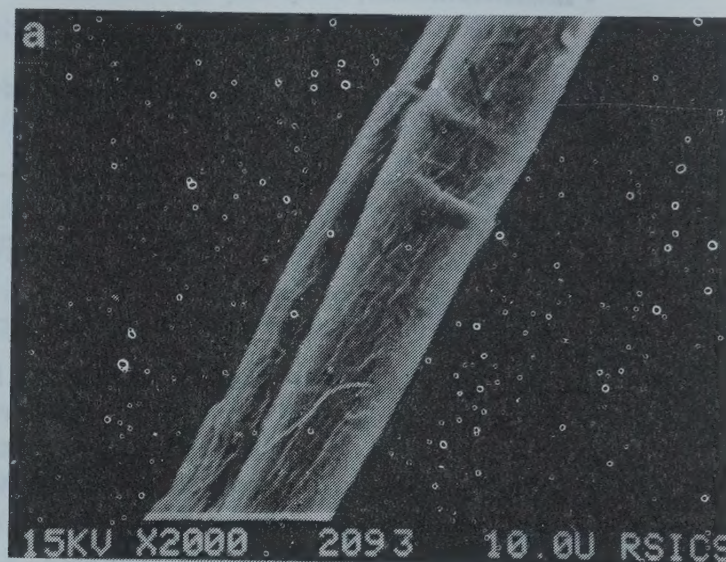
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Newer Antithrombotic Drugs for Prophylaxis of Myocardial Infarction and Stroke

Doodipala Samba Reddy

Department of Pharmacology, University Institute of Pharmaceutical Sciences, Panjab University,
Chandigarh 160 014, India

The present review critically summarizes some of the recent work on various newer antithrombotic drugs for secondary prophylactic use in myocardial infarction and other arterial thromboembolic disorders, including percutaneous transluminal coronary angioplasty and cardiopulmonary bypass, and cerebral stroke. It also focuses on current trends in the development of more selective and potent antiplatelet agents for myocardial infarction.

Introduction

Thrombosis is a major cause of morbidity and mortality worldwide. Thrombus is formed as a pathologic consequence of complex interactions between blood hemostatic mechanisms and components of the injured endothelium of blood vessel. Arterial and venous thrombotic events generally differ from each other. Therefore, type and intensity of antithrombotic approach for coronary thrombosis differs from that of other venous thromboembolic disorders. Antiplatelet agents are effective in the treatment of arterial, whereas anticoagulants are effective in venous thrombosis. Antiplatelet therapy has become a useful means of preventing acute myocardial infarction by inhibiting the activity of circulating platelets as well as the released mediators.

An ideal antiplatelet agent should specifically inhibit platelet-dependent thrombogenic events at injured arterial vessel walls, should be free of toxic effects, should possess sufficient duration of action, should be orally active, and should not interfere with other physiological functions of platelets and wound healing, and should not interact with other components of haemostasis and regional perfusion, and should exhibit sufficient efficacy during and after percutaneous transluminal coronary angioplasty (PTCA) and cardiopulmonary bypass, and should be effective in preventing the development of restenosis following PTCA. Unfortunately, none of the available antiplatelet agents meets all of these criteria. The

antiplatelet effect of aspirin is to permanently acetylate cyclooxygenase and inhibit thromboxane synthesis, without affecting platelet adhesion^{1,2}. Aspirin reduced the incidence of death and progression to definite myocardial infarction in several clinical trials^{3,4}. Aspirin is the standard drug for the long-term oral treatment of secondary prevention of myocardial infarction⁵, and it remained as the basic antiplatelet agent for all kinds of acute interventions involving platelet-dependent thrombotic events, including PTCA and thrombolytic therapy of acute myocardial infarction⁶. However, aspirin is neither selective for the platelet nor a potent antiplatelet agent, and is unable to interfere to any broader extent with the thrombogenic activity of a preexisting clot^{7,8}. Several newer therapeutic alternatives have been developed for prophylactic use in myocardial infarction⁹. Currently, many of these new drugs are under rigorous clinical trials, and may be commercially available in the near future.

Molecular Basis of Thrombosis

Vascular endothelium plays an important role in the maintenance of fluidity of blood by multiple mechanisms. The electronegative charge of the endothelial membrane prevents cell deposition on its surface¹⁰. Endothelial cells rapidly degrade platelet pro-aggregatory adenosine diphosphate (ADP) and also synthesizes prostacyclin, nitric oxide (NO), and 13-hydroxy octadecadienoic acid (13-HODE)¹¹. In-

tact endothelium interrupts fibrin deposition by thrombomodulin-dependent production of activated protein C, which down-regulates thrombin generation, and also by heparin sulphate-dependent antithrombin-III inhibition of thrombin activity. Fibrinolytic mechanisms are also up-regulated by thrombin's direct action on endothelium to release tissue plasminogen activator (t-PA)¹². Moreover, coagulation is controlled by the action of potent plasma serine-protease inhibitors including antithrombin-III, heparin cofactor-II, α_3 -macroglobulin and α_1 -antitrypsin. Finally, activated prothrombotic molecules are diluted into flowing blood and then rapidly removed from the circulation by the tissue mononuclear phagocytic system.

Vascular injury exposes the subendothelium to circulating platelets. Platelets adhere to subendothelial connective tissue elements at sites of endothelial injury, mainly through platelet-von Willebrand Factor (vWF) ligand formation between platelet receptor glycoprotein (GP) Ib and subendothelial collagen^{13,14} (Fig.1). The adhesive proteins, fibronectin, vitronectin, and thrombospondin may also participate in adhesion to subendothelium through platelet GP IIb/IIIa, the common receptor for several adhesive proteins that depends on the tripeptide sequence arg-gly-asp, and GP IV. GP Ia, a putative receptor for collagen, may also have a role for optimal platelet adhesion, and the endogenous production of platelet 12-hydroxyeicosatetraenoic acid (12-HETE) reported to be involved in platelet adhesion as an internal regulator of the expression of adhesion moieties on the platelet surface¹⁰. Platelet adhesion initiates a series of complex interactive platelet recruitment reactions comprising release of dense granule ADP, activation of platelet membrane phospholipase complex to form thromboxane A₂, and release of α -granule binding proteins including

fibrinogen, vWF, fibronectin, vitronectin and thrombospondin¹⁵. Platelet activation depends on an increase in cytoplasmic calcium via activation of phospholipase C-PIP₂-IP₃ pathway. ADP, a potent aggregating agent, is released from the dense granules, binds to its receptor on ambient platelets, decreases cAMP activity and induces GP IIb/IIIa fibrinogen receptor expression resulting in platelet recruitment. The endoperoxide metabolites of arachidonic acid (Fig.2), thromboxane A₂ (TXA₂) and prostaglandin G₂ (PGG₂) are potent platelet agonists involved in the platelet recruitment. Moreover, platelet recruitment requires expression of GP IIb/IIIa as a ligand receptor, and the binding of platelets occurs through calcium-dependent bridging with

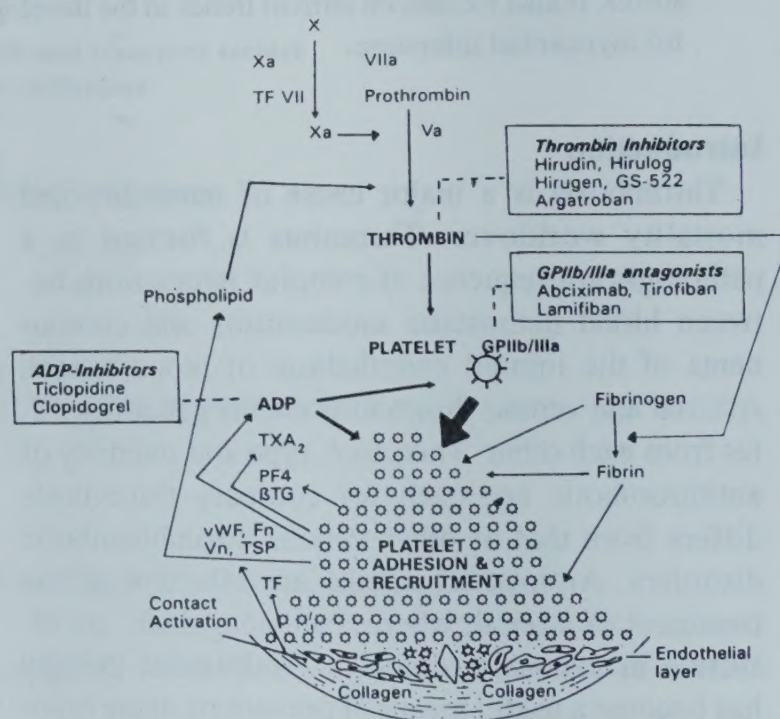
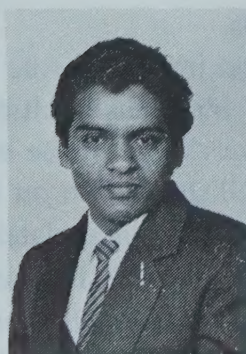


Fig. 1 — Diagrammatic representation of mechanism of thrombosis and potential sites for the action of antithrombotic interventions. The newer antithrombotic drugs in development have been indicated in boxes. The generation and central role of thrombin and platelet adhesion and recruitment are highlighted



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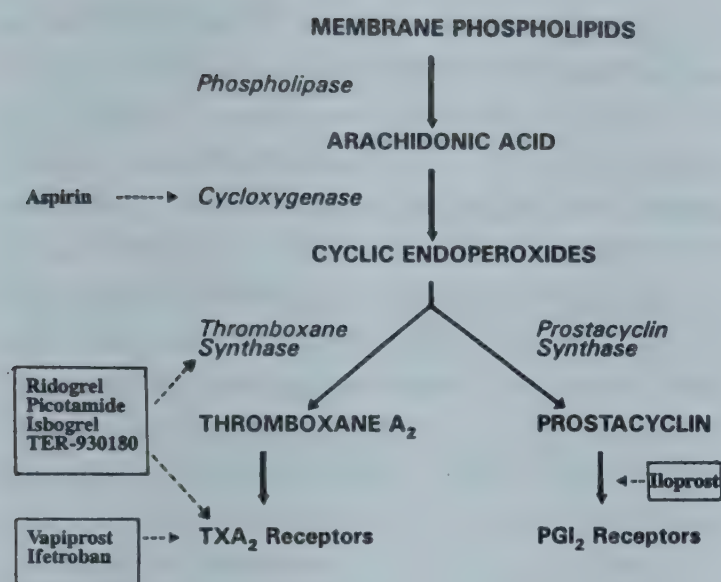


Fig. 2 — Schematic representation of arachidonic metabolism in platelets and potential sites for the antithrombotic intervention. The newer anti-platelet agents in development have been indicated in boxes. The conversion of PGH_2 to PGI_2 and PGD_2 has not been demonstrated to occur within platelets

Table 1- Putative platelet receptors and their ligands

Receptor	Ligand
GP IIa/IIIb	Fibrinogen
GPIa	Collagen
GPIb	vWF
α_2 -Adrenoceptor	Epinephrine Norepinephrine
α_2 -Adrenoceptor	Epinephrine
5-HT ₂	5-Hydroxytryptamine
V ₁ -Vasopressinoceptor	Vasopressin
Imidazoline receptor	Imidazolines

fibrinogen. Platelet cell membrane possesses many receptors in addition to glycoprotein receptors

(Table 1), which have been implicated in the regulation of platelet aggregation. Moreover, abnormalities of platelet cell components (Table 2), also decreases the function of platelets.

Thrombin is the most potent patho-physiological initiator of platelet activation. Thrombin activates platelets independently at concentrations less than that required to convert fibrinogen to fibrin, and augments platelet aggregation through ADP- and TXA_2 -mediated pathways. Thrombin forms on the platelet surface at 300,000-fold increased rate through either intrinsic factor VIIIa-dependent or extrinsic factor Va-mediated pathways. Therefore, thrombin greatly amplifies thrombotic processes by positive feedback mechanisms for both platelets and fibrin. Moreover, the thrombotic mass is consoli-

Table 2 - Disorders of platelet function

Disorder	Reason
Glanzmann's disease	Absence of GPIIb/IIIa receptor complex
Vernard-Soulier syndrome	Absence of GPIb
Von Willebrand's disease	Decreased levels of vWF
Chediak-Higashis syndrome	Granule storage defect

dated by the thrombin- dependent conversion of fibrinogen into fibrin and the activation of factor XIII¹⁰.

Intravascular thrombosis is limited by multiple protective mechanisms. Because thrombin is the pivotal enzyme in the formation of thrombus, it is the principal focus in its regulation. Thrombin initiates antiaggregant, anticoagulant, and profibrinolytic properties of endothelium by multiple mechanisms¹¹. Thrombin stimulates the release of antiaggregant molecules, prostacyclin and nitric oxide, complexes with heparin- like glycosaminoglycans at the surface of the endothelium and facilitates complex formation with antithrombin-III, and inactivates its coagulant and platelet stimulatory capability. Moreover, the thrombin-thrombomodulin complex, with protein S as a cofactor, activates protein C, and activated protein C further destroys platelet-bound factors Va and VIIa activity, thereby down-regulating the production of thrombin. Finally, thrombin activity is inhibited by several plasma serine-protease inhibitors, particularly antithrombin. Additionally, intact endothelium adjacent to forming thrombus inactivates ADP and vasoactive amines released from activated platelets. Therefore, the aim of the antithrombotic interventions, particularly in thromboembolic disorders, is to choose agents with an appropriate ratio of antithrombotic efficacy to hemostatic safety. The antiplatelet agents, which inhibit platelet recruitment into forming thrombus in coronary arteries, are the drugs of choice in the secondary prevention of myocardial infarction.

Inhibitors of ADP-induced Platelet Aggregation

ADP is the pivotal platelet pro-aggregatory molecule. It is normally generated from the ATP during the thrombotic events and vascular vessel wall injury increases the ADP levels locally at the sites of platelet aggregation. ADP-mediated platelet aggregation has

been imputed to the c-AMP-dependent mechanisms, and subsequent activation of intracellular machinery. Dipyridamole is the widely used antiplatelet drug that has been proposed to act partly at least by adenosine-related mechanisms. Consequently, several newer and potent inhibitors of ADP-mediated platelet aggregation have been developed.

Ticlopidine and Clopidogrel

Ticlopidine and clopidogrel are two closely related thienopyridines, which selectively and specifically interfere with ADP-mediated platelet activation and causes an irreversible, non-competitive inhibition of platelet function¹⁶. Typically, ADP is rapidly generated from adenosine triphosphate released from various sources, such as red cells. Moreover, endothelial disruption greatly reduces the ADPase activity, thereby further increases the local levels of ADP at the site of platelet adhesion¹⁷. Ticlopidine and clopidogrel are particularly effective under conditions of shear stress-induced platelet activation and endothelial dysfunction. However, thienopyridines do not affect arachidonic acid metabolism in the platelets.

Ticlopidine and clopidogrel are the pro-drugs, which are inactive *in vitro*. Effective ADP antagonistic effects can be seen after 3-5 d of oral administration, and the effects persist up to about 10 d¹⁸. Thienopyridines are reported either to change the properties of platelet membrane or bind to platelets. Ticlopidine inhibits ADP induced α -granule secretion, which contain fibrinogen, mitogenic factors, P-selectin and other adhesive proteins. Ticlopidine inhibits the AP-induced exposure of the fibrinogen binding site of the GPIIb/IIIa receptor complex by interrupting the mobilization of granules without affecting the receptor complex¹⁹. Ticlopidine and clopidogrel inhibit the 2-methylthio-ADP binding ADP receptors of the platelet membrane, and thereby markedly reduces the platelet cAMP levels.

In several thrombotic models, thienopyridines showed better efficacy than aspirin in preventing the thrombus formation^{20,21}. Ticlopidine and clopidogrel, are particularly effective in preventing stenosis-induced thrombus formation and shear stress-induced platelet aggregation and secretion. However, their antiplatelet effects are reduced in hypercholesterolaemic animals. Clopidogrel effec-

tively antagonised the cyclic flow variations in stenosed coronary arteries in dogs and in femoral artery stenosis and endothelial injury in pigs²². Ticlopidine also facilitates deaggregation of human platelets after aggregation by thrombin. In all animals models, thienopyridines were significantly more potent than aspirin. The antithrombotic efficacy of ticlopidine and clopidogrel were also confirmed in studies in healthy volunteers. The increased shear stress-induced platelet aggregation in patients with atherothrombotic stroke and transient ischemic episodes is corrected by ticlopidine but not by aspirin. Moreover, clopidogrel enhances the effectiveness of fibrinolysis²³. These data suggest that thienopyridines, unlike aspirin, are effective inhibitors of shear stress-induced platelet activation, adhesion and α -granule secretion.

Thienopyridines were studied in several clinical trials²⁴, and found to be effective in secondary prevention of stroke, myocardial infarction and peripheral arterial thrombosis. The Ticlopidine Aspirin Stroke Study and other similar studies also indicated that ticlopidine may be superior to aspirin^{24,25}. The most frequent adverse effect of ticlopidine is diarrhea. Other side effects include urticaria, pruritus, erythema, haemorrhagic epistaxis and menorrhagia. The most serious adverse effect is neutropenia, which is generally reversible upon drug discontinuation. Clopidogrel was developed because this drug was not toxic to bone marrow pluripotent stem cells.

Glycoprotein IIb/IIIa Antagonists

The heterodimer glycoprotein IIb/IIIa receptor complex is a member of integrin superfamily of receptors which mediates platelet aggregation, platelet adhesion to collagen, fibroblast adhesion to fibronectin and vitronectin and leukocyte binding to endothelial cells and matrix proteins²⁶. Platelet activation leads to mobilization of GPIIb/IIIa receptors from internal pools and transition into high affinity state. GPIIb/IIIa ligands such as fibrinogen, wWF, thrombospondin and vitronectin bind at the arg-gly-asp recognition site. GPIIb/IIIa antagonistic ligands have been designed to prevent the fibrinogen binding and linkage of platelets and subsequently prevent platelet aggregation and platelet-dependent thrombus formation. Several classes of inhibitors tested include snake venom, monoclonal antibodies (Table 3), cyclic peptides, arg-gly-asp peptides, and

Table 3 - The monoclonal antibody type inhibitors of glycoprotein IIb/IIIa receptor

Name	Abstract	Ref.
Abciximab	MAB against GP IIb/IIIa for use in PTCA, and treatment of refractory, unstable angina (phase III)	Centocor Lilly & Fujisawa
YM-337	Platelet aggregation inhibitor, Fab fragment of the humanized monoclonal antibody C4G1 that binds to GP IIb/IIIa receptor (preclinical)	Yamanouchi

[Adapted from The R & D Compass Bearing Report (October, 1996), Prouse Science, Barcelona, Spain]

orally active non-peptide antagonists²⁶⁻²⁸. GPIIb/IIIa antagonists are the most powerful agents since all of the different platelet activation pathway finally result in the expression and activation of GPIIb/IIIa receptor, and are more specific than aspirin or thrombin inhibitors.

Abciximab

Abciximab, a murine derived monoclonal antibody, is the first and most extensively investigated inhibitor of GPIIb/IIIa²⁹. Abciximab significantly reduced the cyclic flow variation and occlusion rates in dogs. Moreover, thrombolysis-induced platelet activation has been markedly inhibited by the antagonists of GPIIb/IIIa³⁰. Unlike aspirin, abciximab successfully prevented cyclic flow variations associated with PTCA, and prolonged the bleeding time at 2 h when a bolus injection of 0.25 mg/kg was given³¹. This study reported a 87 per cent inhibition of the platelet GPIIb/IIIa receptor with 88 per cent inhibition of platelet aggregation. Abciximab dose-dependently prolonged the bleeding time and thrombocytopenia, without any spontaneous hemorrhage in patients with unstable angina.

The clinical efficacy of abciximab was extensively studied in patients with acute myocardial infarction, high-risk patients undergoing coronary angioplasty who had unstable angina with recent or evolving myocardial infarction³², and in patients with severe unstable angina refractory to conventional therapy. These studies indicated that abciximab reduces *ex vivo* platelet aggregation to ADP, prolongs bleeding time without excess bleeding, and reduces the rate of acute ischemic complications. Further, the authors have suggested that abciximab is a safe and promising antiplatelet agent. However, they have

warned about its effect causing an increased risk for bleeding thrombocytopenia and suggested an individualized dosage regimen.

Tirofiban and Lamifiban

Tirofiban and lamifiban are nonantibody, orally active antagonists of GPIIb/IIIa receptor complex, which inhibit platelet aggregation at nanomolar concentrations³³. Tirofiban dose-dependently inhibited the platelet aggregation and prolongation of bleeding time in healthy volunteers. Lamifiban and tirofiban are more selective for GPIIb/IIIa than for vitronectin²⁷, and were focused to be more effective than aspirin and hirudin in preventing cyclic flow variation in the guinea-pig artery preparation. Both tirofiban and lamifiban were evaluated for their clinical efficacy³⁴. Although the marked inhibition of the haemostatic function of platelet and a substantial bleeding tendency by these agents may limit their usage, the short duration of action, and rapid reversibility make them superior to aspirin. Moreover, SMART and TIMI-8 trials indicated the occurrence of bleeding events that cannot be predicated from prolongation of bleeding time.

Several novel orally active GPIIb/IIIa antagonists such as fradafiban, SC-54684, GR-1434043, L-703014 are reported to inhibit platelet aggregation at micromolar concentrations with relatively long duration of action. However, further studies are needed to establish their clinical efficacy. In contrast, several glycoprotein Ib antagonists, which are under exploration, have shown only moderate antithrombotic activities. Currently, several other GPIb antagonists have been tested in various laboratories for their possible antithrombotic activities. Since fibrinogen is a pivotal endogenous ligand for the GPIIb/IIIa

Table 4 - Compendium of most recently described fibrinogen receptor antagonists for treatment of disorders of the coronary arteries and thrombotic conditions

Name	Characteristics	Ref.
Fradafiban BIBU-52	Platelet aggregation inhibitor (Phase II)	Dr. Karl Thomae- Boehringer Ingelheim
C68-22 Integrelin	Platelet aggregation inhibitor for reducing complications of coronary angioplasty, and for unstable angina and acute myocardial infarction (Phase II)	COR Therapeutics & Schering-Plough
DMP-728 S	Small peptide for unstable angina and angioplasty, and adjunct to thrombolysis (phase I)	DuPont Merck
DMP-754	Antithrombotic (preclinical)	DuPont Merck
XR-300	Orally active prodrug (preclinical)	DuPont Merck
FK-633	Antithrombotic (phase II)	Fujisawa
GR-164053	Platelet aggregation inhibitor	Glaxo Wellcome
G-7446	Antithrombotic (preclinical)	Alpha Therapeutic- Green Cross & Roch
G-7453	Platelet aggregation inhibitor (preclinical)	Alpha Therapeutic- Green Cross
Ro-48-3657	Double prodrug related to lamifiban (preclinical)	Alpha Therapeutic- Green Cross & Roch
TP-9201	Platelet aggregation inhibitor for acute thrombotic disorders (phase I)	Telios-Integra Life Sciences
RWJ-50042	Platelet aggregation inhibitor (preclinical)	R.W. Johnson-Johnson & Johnson
ME-3277	Platelet aggregation inhibitor (preclinical)	Meiji Seika
L-709780	Antithrombogenic agent (preclinical)	Merck & Co.
L-734217	Platelet aggregation inhibitor (preclinical)	Merck & Co.
Tirofiban MK-383	Antiplatelet, for reducing risk of cardiac events during balloon angioplasty and for unstable angina (Phase III)	Merck & Co.
SC-52012	Platelet antiaggregatory agent (phase I)	Searle-Monsanto
Xemilofiban SC-54684	Orally active antithrombotic for angioplasty, acute Myocardial infarction and unstable angina (phase I)	Searle-Monsanto & Sankyo
RG-13965	Platelet aggregation inhibitor (preclinical)	Rhone-Poulenc Rorer
RPR-109891	Orally active fibrinogen receptor antagonist (phase II)	Rhone-Poulenc Rorer
RPR-110173	Antithrombotic (research)	Rhone-Poulenc Rorer

-- Contd

Table 4 - Compendium of most recently described fibrinogen receptor antagonists for treatment of disorders of the coronary arteries and thrombotic conditions

		-- (Contd)
Name	Characteristics	Ref.
G-7446	Antiplatelet, fibrinogen receptor antagonist (preclinical)	Roche
Lamifiban Ro-44-9883	Platelet antiaggregator agent for acute coronary syndrome (phase III)	Roche
Xemilofiban	Orally active antithrombotic (phase II)	Sankyo & Searle
SB-214857	Orally active fibrinogen receptor antagonist (preclinical) for thrombotic disorders	SmithKline Beecham
PS-028	Nonpeptide selective fibrinogen receptor antagonist (preclinical)	Taisho
TAK-029	Orally active fibrinogen receptor antagonist (phase I)	Takeda
TRM-147	Orally active fibrinogen receptor antagonist (preclinical)	Terumo
TRM-153	Antithrombotic, fibrinogen antagonist (preclinical)	Terumo

[Adapted from The R & D Compass Bearing Report (October, 1996), Prouse Science, Barcelona, Spain]

receptor complex, several fibrinogen antagonists have been under accelerated development (Table 4) for use in various arterial occlusive and thrombotic disorders. It is hoped that they would provide superior and effective antithrombotic efficacy over aspirin in clinical trials.

Thromboxane Synthase/Receptor Inhibitors

The fact that aspirin, by preventing thromboxane A_2 (TXA_2) formation in platelets by means of cyclooxygenase inhibition, is effective in the secondary prevention of myocardial infarction, and other vascular occlusive disorders, has led to design agents interfering directly with thromboxane formation and/or action. Several potent and selective TXA_2 synthase inhibitors and TXA_2 receptor antagonists have been developed³⁵. Thromboxane synthase inhibitors, as a result of preventing TXA_2 formation selectively, redirect an intermediate prostaglandin endoperoxide (PGH_2) metabolism towards the increased formation of PGI_2 and PGD_2 , with the accumulated PGH_2 causing strong platelet aggregation and vasoconstriction by binding to TXA_2 receptors on the platelet membrane³⁶. Thus, the lack of antiplatelet and antithrombotic efficacy of thromboxane

synthase inhibitors has been suggested as being due to the accumulation of PGH_2 . Therefore, most thromboxane synthase inhibitors have a moderate potency, a short duration of action, and do not result in a sufficiently sustained inhibition of TXA_2 production, and have shown discouraging clinical efficacy in patients with coronary artery disease.

Thromboxane receptor antagonists have been developed recently which specifically impede the action of both TXA_2 and endoperoxides on their presumed common receptors on platelets and prevent vasoconstriction induced by TXA_2 . Moreover, TXA_2 synthesis is not affected and PGI_2 generation is not enhanced with specific thromboxane receptor antagonists. Thromboxane receptor antagonists, being potent inhibitors of PGH_2/TXA_2 induced platelet aggregation, have shown superior antithrombotic effects in several animal models and some are currently undergoing clinical trials³⁷ (Table 5). However, these drugs only preserve rather than increase the endogenous production of platelet inhibitory prostaglandins and do not affect platelet aggregation induced by TXA_2 -independent agonists, such as high-dose collagen, thrombin and ADP.

In contrast, a combination of thromboxane recep-

Table 5 -- Compendium of the newer thromboxane synthase and receptor inhibitors under development for treatment of disorders of the coronary arteries and platelet-dependent thrombotic events

Name	Characteristics	Ref.
Isbogrel	Thromboxane A ₂ synthase inhibitor, treatment of ischemic attacks (clinical)	Abbott & Takeda
DTTX-30	Thromboxane/endoperoxide receptor antagonist and thromboxane A ₂ synthase inhibitor (phase I)	Dr. Karl Thomae - Boehringer Ingelheim
BIBV-308	Thromboxane A ₂ antagonist and thromboxane A ₂ synthase inhibitor, treatment for thromboembolic diseases (phase II)	Boehringer Ingelheim
Ifetroban	Thromboxane A ₂ /prostaglandin endoperoxide receptor antagonist for unstable angina, heart attack, intermittent claudication (phase II)	Bristol-Myers Squibb
LCB-2853	Platelet antiaggregatory and antivasospastic agent, TX A ₂ / PGH ₂ antagonist for unstable angina, restenosis, and atherosclerosis (preclinical)	Lipha-E. Merck
Camonagrel FI 2845	Thromboxane synthase inhibitor, antithrombotic (phase II)	Ferrer
Vapiprost SN-309	Thromboxane A ₂ antagonist for chronic arterial occlusive diseases (Phase III)	Glaxo Wellcome
NM-702	Phosphodiesterase III and V inhibitor and thromboxane A ₂ synthase inhibitor (preclinical)	Green Cross & Nissan Chemical
Ridogrel R-68070	Thromboxane A ₂ synthase/receptor dual inhibitor, adjunct to thrombolysis in myocardial infarction (phase II)	Janssen-Johnson & Johnson
KDI-792 FK-070	Thromboxane A ₂ antagonist and thromboxane synthase inhibitor for peripheral circulatory disorders (phase II)	Kissei & Fujisawa
KT-2692	Thromboxane A ₂ antagonist, azulene derivative (phase I)	Kotobuki
KF-13218	Thromboxane A ₂ synthase inhibitor (preclinical)	Kyowa Hakko
C85	Antiplatelet, inhibit thromboxane A ₂ production and phosphoinositide breakdown (preclinical)	National Defense Medical Center
Linotroban HN-11500	Thromboxane A ₂ antagonist, prevention of blood clots (phase II)	Nycomed
TER-930180	Antithrombotic, thromboxane A ₂ antagonist and thromboxane A ₂ synthase inhibitor (preclinical)	Terumo
Z-335	Platelet aggregation inhibitor, thromboxane A ₂ antagonist	Zeria

[Adapted from The R & D Compass Bearing Report (October, 1996), Prouse Science, Barcelona, Spain]

tor antagonists and thromboxane synthase inhibitors has been demonstrated to be more efficacious *in vitro* than either agents alone or aspirin in human whole blood³⁸. The mode of synergistic effect, to block PGH₂/TXA₂ receptor transducing platelet aggregation and vasoconstriction, as well as to augment this antithrombotic effect with the help of increased levels of PGI₂ and other anti-aggregating prostaglandins, has been confirmed in both animal models³⁹ and in clinical trials. Recently, several inhibitors possessing dual TXA₂ synthase inhibiting and TXA₂ receptor antagonistic activities have been reported⁴⁰ (Table 5).

Vapiprost and Ifetroban

Vapiprost and ifetroban are potent and long acting thromboxane receptor antagonists³³. Several comparative studies in animal models of arterial thrombosis have found vapiprost or ifetroban to be more effective than antithrombin hirudin, and aspirin in preventing cyclic flow variations. Moreover, the antithrombotic efficacy of ifetroban was only partially reduced by epinephrine though inhibition of thrombus formation was less than that seen with the direct thrombin inhibitors. Although both these compounds failed to show any advantage over the aspirin in initial clinical trials, their precise clinical antithrombotic efficacy remains to be determined.

Ridogrel and Picotamide

Ridogrel and picotamide are thromboxane synthase and receptor dual inhibitors. Ridogrel is a potent TXA₂ synthase inhibitor with modest TXA₂/PGI₂ receptor antagonist properties³³. Ridogrel prevents the arterial thrombosis induced by deep vessel wall injury in animals. In contrast, picotamide is a weak thromboxane synthase inhibitor and thromboxane receptor blocker. Unlike aspirin, picotamide was recently found to reduce platelet deposition to injured vessel segments *ex vivo*. In one large-scale controlled clinical study, ridogrel was compared with aspirin in patients with acute myocardial infarction and treated with streptokinase⁴¹. Ridogrel was found to be more effective in preventing new ischemic episodes, but not superior to aspirin in enhancing the fibrinolytic activity of streptokinase.

TER-930180

TER-930180 is a recently reported selective, po-

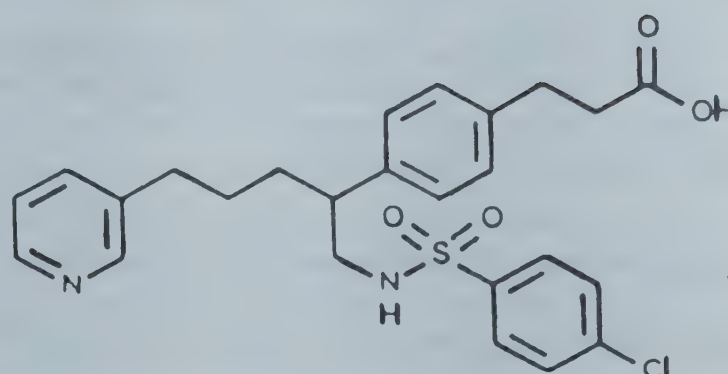


Fig. 3 — Chemical structure of TER 930180, a thromboxane A₂ synthase/receptor dual inhibitor

tent and long- acting dual TXA₂ synthase and thromboxane receptor inhibitor. TER-930180, [3-{4-[1-(4-chlorophenyl-sulphonamido-dimethyl)-4-(-3-pyridyl)butyl]-phenyl}propionic acid], showed potent antithrombotic effect in several animals models of arterial thrombosis⁴² (Fig.3), as well as in *ex vivo* and *in vitro* models of platelet aggregation. The antithrombotic effect appears to be due to its ability to increase in anti-aggregating and vascular relaxing prostanoids mediated by endoperoxide steal, in addition to its inhibitory action of PGH₂/TXA₂-induced platelet aggregation and shape change. Several other dual inhibitors with potent and equal activity such as CGS-22652, KDI-792 and ICI-D452 have been reported (Table 5). However, there is no published data on their clinical potency in arterial occlusive disorders.

Prostacyclin Mimetics/Releasers

Prostacyclin, a potent endogenous inhibitor of platelet aggregation, inhibits cyclic flow variations in stenosed coronary arteries by elevating the cAMP content of platelets and subsequent stimulation of cAMP-dependent protein kinases and calcium uptake into intracellular stores. However, many prostacyclin mimetics such as iloprost, cicaprost, and taprostene showed nonspecific effects and low selectivity for the platelet. Moreover, increase in prostacyclin levels is known to associate with the down-regulation of prostacyclin receptors in several arterial occlusive disorders. Although all the available prostacyclin mimetics may not desensitize platelets, limited selectivity, short duration and narrow therapeutic window of prostacyclin mimetics re-

Table 6 -- Compendium of various newer prostacyclin analogues and related agents under development for treatment of disorders of the coronary arteries and platelet-dependent thrombotic events

Name	Characteristics	Ref.
Pamcogrel	Cyclooxygenase inhibitor (phase III)	Torri-Asahi Brewery
Lipo-alprostadi	Liposomal prostaglandin for venous insufficiency (phase III)	Knoll-BASF Green Cross/Taisho
Beraprost	Prostacyclin derivative for intermittent claudication (phase II)	Bristol-Myers Squibb
Satigrel E-5510	Platelet antiaggregatory and antithrombotic agent, cyclooxygenase and phospholipase inhibitor (phase II)	Eisai
FR-12207	Cyclooxygenase inhibitor (preclinical)	Fujisawa
Taprostene	Stable prostacyclin analog for peripheral arterial disease (phase III)	Gruenenthal
LM-AS-013	Liposomal PGE1 prodrug for vascular disorders (phase II)	Green Cross & Seikagaku
Pamcogrel KBT-3022	Antiplatelet and cyclooxygenase inhibitor (phase III)	R.W. Johnson- Johnson & Johnson
KC-764	Cyclooxygenase inhibitor, antithrombotic (phase I)	Kyorin
ONO-1301	Orally active non-prostanoid prostacyclin mimetic and thromboxane A ₂ synthase inhibitor (phase I)	Ono
Beraprost RU-55100	Orally active prostacyclin analog, antiplatelet and vasodilator treatment for intermittent claudication (phase III)	Roussel Uclaf Toray
SI-1702	PGE1 prodrug (phase II)	Seikagaku & IMS Saint Marianna Uni.
TEI-8535	Thia-prostaglandin F1 derivative, inhibitor of MCP-1-induced chemotaxis, treatment of atherosclerosis	Teijin

[Adapted from The R & D Compass Bearing Report (October, 1996), Prouse Science, Barcelona, Spain]

stricts their usage in the prophylaxis of myocardial infarction (Table 6).

Iloprost

Iloprost is a potent, stable analogue of prostacyclin with encouraging antithrombotic efficacy in several animals models⁴³. It is a potent inhibitor of platelet activation in nanogram concentrations, and also abolishes the pro-aggregation of platelets by ADP, collagen and epinephrine. However, iloprost was unable to prevent re-occlusions of stenosed dog coronary arteries after electrical injury and thrombolysis. Since iloprost is also an arterial vasodilator and thus produces severe hypotension upon systemic administration. Several prostacyclin derivatives such as ci-

caprost, beraprost and others are undergoing clinical trials, and will be available in the near future (Table 6).

Defibrotide

It is a sodium salt of a single-stranded oligonucleotide with antithrombotic activity, partly at least by prostacyclin related mechanisms⁴⁴. Thus, it can be grouped under the aptameric oligonucleotides, which binds to and modulate several functional proteins and receptor systems in a sequence-independent manner⁴⁵. Defibrotide, which is devoid of anticoagulant properties, stimulates PGI₂ and PGE₂ production without affecting TXA₂ levels, and also activates the fibrinolytic system. Several other mechanisms for

defibrotide have been recently proposed, including the stimulation of thrombomodulin expression. Preliminary studies indicated a favourable antithrombotic efficacy for defibrotide, however, more studies are needed to evaluate its efficacy in myocardial infarction.

Thrombin Inhibitors

Thrombin is a serine protease which converts fibrinogen to fibrin and activates platelets and clotting factors V, VII, XI and XIII¹³. It is the multifunctional protein involved in the platelet-dependent thrombotic vessel occlusion at sites of atherosclerotic stances and plaque rupture⁹. Currently, there is an intensive search for the development of selective, and directly acting thrombin inhibitors with a shorter duration of action than heparin, and with fewer side effects⁴⁶ (Table 7). In patients receiving cardiopulmonary bypass, aspirin, prostacyclin, prostacyclin analogs and thromboxane synthase inhibitors have been used with thrombin inhibitors to reduce the platelet dysfunction. Thus, direct-acting thrombin inhibitors are a new class of antithrombotic agents that can act on both free and clot-bound thrombin, thereby interfering with the central component of the coagulation cascade and exhibit additional beneficial effects.

Heparin, the widely used anticoagulant, accelerates the inhibition of thrombin by its natural plasma inhibitor antithrombin III. In addition to causing bleeding complications, it may cause other problems as well. Heparin is not effective in treating arterial thrombosis, probably because of resistance of thrombin bound to fibrin clots on the exposed subendothelial matrix to hepatic-antithrombin III inhibition. Moreover, heparin produces thrombocytopenia, and when heparin is used in cardiopulmonary procedures, protamine sulphate is used to reverse its anticoagulant effect, which is associated with hypotension and myocardial depression^{47,48}. Several low molecular weight heparins and heparin-like compounds have also been studied (Table 7). Thus, the search continues for a better thrombin inhibitor with a shorter duration of action.

Hirudin

Hirudin, the reference antithrombin, is obtained from the salivary glands of leech *Hirudo medicinalis* and produced on large-scale by recombinant technol-

ogy⁴⁹. It is a 65 amino acid single-chain polypeptide containing three intramolecular disulphide bridges and a sulphated tyrosine residue. Hirudin is a specific, potent and direct inhibitor of thrombin by binding at the anion-binding exosite on thrombin. It prevents thrombin induced aggregation but not other platelet agonists, and has bioavailability of more than 80 per cent after subcutaneous injection. However, the results are not encouraging in several double-blind, multicentre clinical studies in patients with angina undergoing PTCA, unstable angina and angiographic thrombus, myocardial infarction, and coronary bypass procedures⁵⁰. In some of these studies, even the bleeding times were not significantly prolonged. Hirudin at 0.1mg/kg/h appeared to be as efficacious in the unstable angina, and the TIMI-5 pilot studies. High bleeding risk and haemorrhagic shock appeared to be apparent in several clinical trials³³. Many of these studies stimulated for searching more specific and direct thrombin inhibitors superior to heparin and hirudin.

Hirulog

This bifunctional 20-amino acid polypeptide consists of a C- terminus fragment of hirudin that interacts with the anion- binding exosite of thrombin, and a N-terminus phe-pro-arg-pro-gly fragment, which interacts with the catalytic site of thrombin³³. The hirulog-thrombin interaction is transient with a half-life of about 40 min. Clinical studies indicated a dose-dependent prolongation of the activated partial thromboplastin time (APTT) without significantly altering the bleeding times. The APTT in angina-free patients averaged 55.6 s after 1mg/kg/h of hirudin, and significantly reduced the rate of mortality in myocardial infarcted patients. It can also be employed as an adjunct in thrombolytic therapy⁵¹. More recently, Theroux *et al*⁵² have studied the angiographic patency of the culprit coronary artery lesion 90 and 120 after the initiation of streptokinase and aspirin, and again after 4 d in patients with acute myocardial infarction. Hirulog yielded higher early patency rates than heparin when given as adjunctive therapy to streptokinase and aspirin in the early phase of acute myocardial infarction. In a multicentre trial, hirulog showed a dose-related increase in APTT prolongation without significant bleeding.

Hirugen

Hirugen is a dodecapeptide comprising 12 termi-

Table 7 -- Compendium of various newer thrombin inhibitors and other anticoagulants under development for treatment of disorders of the coronary arteries and diverse thrombotic events

Name	Characteristics	Ref.
Org-31540 SR-90107A	Natural pentasaccharide with high affinity for antithrombin III treatment for deep vein thrombosis (phase II)Elf	Organon-Akzo & Sanofi
Desmin-370	Low-molecular-weight dermatan sulfate for venous thrombosis (phase III)	Alfa-Wassermann & Opocrin
NAPc2	Small protein anticoagulant isolated from the blood-feeding hookworm <i>Ancylostoma caninum</i> and prepared by recombinant techniques that specifically inhibits the enzymatic complex of factor VIIa and tissue factor, lead candidate for the treatment of deep vein thrombosis, pulmonary embolism, unstable angina and heart attack	Immunex-American Home Products & Corvas
Ardeparin	Low-molecular-weight heparin for orthopedic use	Wyeth-Ayerst-AH Products
AT-908 ART-123	Recombinant human urinary thrombomodulin for disseminated intravascular coagulation (phase II)	Asahi Chemical
Inogatran H-314/27	Thrombin inhibitor peptide for acute myocardial infarction, and unstable angina (phase II)	Astra
Melagatran H-319/68	Thrombin inhibitor for myocardial infarction, unstable angina and sudden death	Astra
LU-57291	Polyethylene glycol-modified hirudin mutein, for unstable angina and for use in coronary bypass surgery (phase I)	Knoll-BASF
Factorex	Anticoagulant, factor Xa inhibitor (preclinical)	Bio-Cardia
BMS-186282	Highly-selective thrombin inhibitors (research)	Bristol-Myers Squibb
BMS-189090	Highly-selective thrombin inhibitors (research)	Bristol-Myers Squibb
Desirudin	Genetically engineered hirudin for deep vein thrombosis (NDA)	Ciba-Geigy
12D10 Corsevin M	MAB that recognizes factor VIIa, treatment of acute arterial thrombosis and unstable angina (phase II)	Corvas Centocor
Cordecin AS Corsevin AS CVS-1123	Factor Xa inhibitor, anticoagulant for thrombotic disorders Protein inhibitor of factor VIIa, antithrombotic (preclinical) Orally active small-molecule thrombin inhibitor (phase I)	Corvas Corvas Corvas & Schering-Plough
CVS-995	Highly potent oral thrombin inhibitor (phase I)	Corvas & Corthrombin
XQ-222	Baropeptide thrombin inhibitor (research)	Schering-Plough DuPont Merck
SR-32701	Anti-Xa synthetic pentasaccharide, for prevention of thrombo-embolic diseases (preclinical)	Elf Sanofi
CY-222	Low-molecular-weight heparin for antithrombotic therapy (phase III)	Choay-Elf Sanofi
Baciparcil Iliparcil	Venous antithrombotic, phenylthioxyloside deri. (Preclinical) Venous antithrombotic, phenylthioxyloside deri. (Preclinical)	Fournier Fournier

-- Contd

Table 7 -- Compendium of various newer thrombin inhibitors and other anticoagulants under development for treatment of disorders of the coronary arteries and diverse thrombotic events

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Name	Characteristics	Ref.
Efegatran	Thrombin inhibitor for atherosclerosis, coronary artery disease, and angina (phase II)	Godeon Richter
Argatroban	Synthetic thrombin inhibitor (phase II)	Genentech
Lepirudin	Genetically engineered hirudin for acute myocardial infarction unstable angina pectoris, and arterial and venous thrombosis (phase III)	Hoechst
CRC-220	Antithrombotic, thrombin inhibitor (preclinical)	Bohringwerke-Hoechst
SEL-2711	Specific, orally active, active-site inhibitor of factor Xa for arterial and venous thrombotic disorders (preclinical)	Selectide-Hoechst
SEL-2906	Orally active low-molecular-weight factor Xa inhibitor (preclinical)	Selectide-Hoechst
Certoparin	Low-molecular-weight heparin for peri and postoperative venous thromboembolism	Alpha Therapeutic
GS-522	Thrombin aptamer, oligodeoxynucleotide with a very short half-life thrombin inhibitory activity for use in cardiopulmonary bypass surgery (preclinical)	Green-Cross & Sandoz Gilead
ITF-1300	LMW heparin-diamine complex (preclinical)	Italfarmaco
RWJ-27755	Anticoagulant, thrombin inhibitor (preclinical)	R.W.Johnson-Johnson & Johnson
CX-397	Antithrombotic, recombinant hirudin analog (preclinical)	R.W.Johnson-Johnson & Johnson
Danaparoid sodium	LMW glycosaminoglycan for deep vein thrombosis (phase III)	R.W.Johnson-Johnson & Johnson
Efegatran sulfate	Thrombin inhibitor for coronary artery and angina (phase II)	Lilly & Gedeon Richter
LY-293435	Thrombin inhibitor (preclinical)	Lilly
LY-296516	Tripeptide thrombin inhibitor (preclinical)	Lilly
LY-329186	Antithrombotic, thrombin inhibitor (preclinical)	Lilly
Argatroban	Antithrombotic, synthetic thrombin inhibitor for treatment of heparin-induced thrombocytopenia and thrombolysed myocardial infarction (p-II)	Synthelabo
Reviparin	LMW heparin for deep vein thrombosis (phase II)	Mitsubishi
MR-33	Recombinant human urinary thrombomodulin (phase II)	Mitsui Toatsu & Knoll Mochida
TFPI	Tissue factor pathway inhibitor, anticoagulant, treatment for thrombotic disorders, trauma and critical care (phase II)	Searle-Monsanto & Chiron
NSL-9403	Antithrombotic and anticoagulant peptide comprising RGD as the basic skeleton (research)	Nippon Steel
Napsagatran	LMW thrombin inhibitor (phase II)	Roche
Ro-46-6240		
Ro-11	Low-molecular weight heparin (phase II)	Rovi
SDZ-MTH-958	Antithrombotic, LMW thrombin inhibitor (Preclinical)	Sandoz
Aprosulat sodium	Antithrombotic synthetic polyanion, anticoagulant (phase I)	Luitpold-Sankyo
LW-10082		
S-18326	Tripeptide bornonic acid thrombin inhibitor (preclinical)	Servier
LEX-026	Plasmin inhibitor and thrombin inhibitor, treatment for coagulation disorders	Lexin-Spara
CTC-111	Human activated protein C concentrate, treatment for disseminated intravascular coagulation (phase III)	Teijin

[Adapted from The R & D Compass Bearing Report (October, 1996), Prouse Science, Barcelona, Spain]

nal residues of hirudin in an ion-binding blockade and a sulphated tyrosine. It competitively inhibits thrombin and platelet activation⁵³, and prevents platelet deposition in chronic arteriovenous shunts of baboons. Although hirugen has been claimed to inhibit platelet deposition on highly thrombogenic surfaces, it is a poor antithrombotic agent compared to other direct thrombin inhibitors.

Argatroban

It binds to thrombin and competitively inhibits fibrinogen cleavage and platelet activation. This arginine-derivative is very effective in platelet-rich thrombi⁵⁴, and augmented re-perfusion in stenosed femoral arteries of rabbits. When administered alone or in combination with TXA₂ antagonist, argatroban accelerated the thrombolytic effects of alteplase in stenotic canine coronary model, and in endothelial injury induced coronary thrombus model⁵⁵. Thus, a combination argatroban and aspirin may yield favourable antithrombotic efficacy⁵⁶.

GS-522

Thrombin aptamers based on single-stranded DNA molecules represents a new class of thrombin inhibitors with potent anticoagulant and antithrombotic properties. GS-522 is such a direct thrombin inhibitor that is being tested as an anticoagulant⁵⁷. It is a 15-mer single-stranded oligo-deoxy ribonucleotide with the sequence GGTTGGTG-TGGTTGG. This is the first aptameric oligonucleotide discovered with high affinity for thrombin. Several reports on its chemistry, structure, binding and other characteristics have been reported recently^{58,59}. GS-522 binds to -thrombin at the anion exosite of thrombin which usually binds heparin⁶⁰.

Li *et al.*⁶¹ have reported the efficacy of GS-522 in inhibiting clot-bound thrombin activity and platelet thrombus formation in a whole artery angioplasty model. Griffin *et al.*⁶² studied the anticoagulant properties of GS-522 in one lamb and in seven cynomolgus monkeys *in vivo*. It was concluded that GS-522 is a potent anticoagulant *in vivo*, and specifically inhibits thrombin-induced platelet aggregation *ex vivo*. The rapid onset of action and short half-life suggests that GS-522 may be useful in anticoagulation with extracorporeal circuits and may have distinct advantages in certain acute clinical settings. DeAnda *et al.*⁶³ studied the anticoagulant efficacy of

GS-522 use during cardiopulmonary bypass in 11 mongrel dogs, and suggested that GS-522 is both safe and effective as an anticoagulant in short-term cardiopulmonary bypass model with a reproducible pharmacokinetics. This potential thrombin aptamer may be useful in cardiopulmonary bypass procedures.

DuP-714

It is another direct thrombin inhibitor consisting of baroarginine tripeptide that binds with moderately high affinity to thrombin⁶⁴. It is an effective anticoagulant but has a longer biological half-life than might be desired. Also it reacts with other serine proteases which might pose problems. Its high liver toxicity severely restricts its further studies.

Future Developments

Thrombosis is a complex process with many sites for potential intervention. With the development of new understanding of the complex systems for activation and inactivation of various pathways and the capability of molecular biology to produce many new specific and potent, genetically engineered therapeutic molecules, antithrombotic therapy is likely to undergo substantial innovation in the near future. Apart from the inhibitors of ADP-mediated platelet aggregation, GPIIb/IIIa receptor antagonists, thrombin and thromboxane inhibitors, many more new compounds, which are interesting alternatives or adjuncts have been developed^{9,26,65}. These include thrombomodulin (an endogenous thrombin complexing peptide), protein C (an endogenous inhibitor of thrombin generation), antithrombin III (a natural inhibitor of thrombin), danaparoid sodium (a low molecular weight heparinoid), and tick anticoagulant peptide and antistasin (factor Xa inhibitors) (Table 7), and several mixed action antithrombotics (Table 8), respectively. However, many of these potential antithrombotic agents are not active orally and have limited efficacy. Moreover, some of them have been shown to interfere with the natural mechanisms of hemostatic homeostasis. Future developments include more selective and combined-mode thromboxane inhibitors, long acting, non-peptide, orally active thrombin inhibitors, non-peptide fibrinogen receptor antagonists and molecular biology based aptameric oligonucleotides that specifically bind to thrombin. However, whether these newer

Table 8 -- Summary of mixed antithrombotic agents under preclinical and clinical development

Name	Description	Ref.
AP-1067	Antihypertensive and antithrombotic, dual action calcium channel blocker and 5-HT ₂ antagonist (preclinical)	Abbott
L-103	Platelet aggregation inhibitor, staurosporine analog (research)	Asahi Chemical
ARL-67085	Antithrombotic agent, ATP analog with high affinity for platelet P ₂ -purinoceptors (phase I)	Astra & Fisons
Aspalatone	Platelet aggregation inhibitor, salicylic acid-maltol conjugate (preclinical)	Bukwang & Seoul Uni.
HFV-1017	Antithrombotic, platelet aggregation inhibition, sulfonamide derivative (preclinical)	Fuji Pharmaceutical
GL-2021	Methyl ether derivative of GL-522-Y-1, orally active anti-thrombotic agent (preclinical)	Genelabs Tech.
GL5-522-Y-1	Polysulfonate, oral active antithrombotic agent	Genelabs Tech.
SK-827	Human urine kallikrein, peripheral circulation improver, and treatment for chronic arterial obstruction (NDA)	Nippon Chemiphar Sanwa Kagaku
PN-27.1	Platelet aggregation inhibitor and aortic smooth muscle cell proliferation inhibitor that acts through both the arachidonic acid-induced and PAF pathways, restenosis inhibitor for use in angioplasty procedures (phase II)	Paracelsian
Diadenosine tetraphosphate	Platelet aggregation inhibitor (preclinical)	PRP Worcester Foundn.
Anagrelide	Platelet aggregation inhibitor, phosphodiesterase III inhibitor	Roberts
TA-993	Platelet aggregation inhibitor, weak calcium channel blocker, treatment of peripheral circulatory disorders	Tanabe Seiyaku
AO2131-1	Phosphodiesterase V inhibitor, treatment of thrombotic disorders (preclinical)	Yung Shin

[Adapted from The R & D Compass Bearing Report (October, 1996), Prouse Science, Barcelona, Spain]

agents shows clinical benefits with low risks of bleeding tendencies is a matter of conjecture and large-scale clinical studies can only reinforce some of these interpretations. Nevertheless, a combination of newer agents and currently available agent may optimize efficacy and safety for the prophylaxis of myocardial infarction.

Conclusions

Antithrombotic therapy is a rational means of preventing acute myocardial infarction and other

thromboembolic diseases. Platelet adhesion and recruitment plays a critical role in thromboembolic disorders, while thrombin is the most important pathophysiological initiator of platelet recruitment. Currently, aspirin, a selective inhibitor of platelet aggregation mediated through activation of the arachidonic-thromboxane pathway, is the primary drug of choice for the long-term oral secondary prophylaxis of myocardial infarction. However, it is neither potent nor specific for the platelets, and its efficacy in percutaneous transluminal coronary

angioplasty and platelet activation during clot lysis is relatively poor. Several lines of research towards development of newer antithrombotic agents are being explored including the inhibitors of ADP-mediated platelet aggregation ticlopidine and clopidogrel, glycoprotein IIb/IIIa antagonists abciximab, tirofiban and lamifiban, dual action thromboxane synthase and receptor inhibitors TER-930180, ridogrel and picotamide, prostacyclin analogue iloprost, endogenous prostacyclin releaser defibrotide, low molecular weight heparinoids such as danaparoid sodium, thrombin inhibitors hirudin, hirulog, hirugen, argatran and GS-522, and several other natural and recombinant peptide inhibitors of coagulation, respectively. Aptameric single-stranded oligonucleotides have been developed as direct thrombin inhibitors. New compounds such as ticlopidine, abciximab, iloprost, defibrotide, sulodexide and hirudin analogues have shown promise in both animal models and several clinical studies. Ticlopidine analogue clopidogrel does not have toxic effect on bone marrow pluripotent stem cells. Cyclic peptides and small molecules may prove to be better antithrombotic agents and have no risk of immunogenicity. These new compounds are highly potent in preventing platelet-dependent re-occlusion and are superior to aspirin in acute platelet-dependent ischemic syndromes. However, more clinical trials are needed to determine whether these compounds provide superior efficacy over aspirin in the secondary prophylaxis of myocardial infarction and other thrombotic conditions.

Acknowledgements

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Homogeneous and Heterogeneous Nickel Catalysts : Some Important Industrial Applications

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Recent developments in the area of Ni-catalyzed homogeneous and heterogeneous reactions are summarized keeping in view their applications to chemical process industry. Some industry relevant reactions such as carbonylation and polymerization (oligomerization, dimerization and cyclization) catalyzed by homogeneous organo-Ni complex catalysts and hydrogenation of organic compounds with various functional groups using supported Ni catalysts are elucidated. A new class of Ni catalysts with suitable chiral modifiers used for the synthesis of enantioselective products is also described.

Introduction

Catalysis and catalytic processes have made significant impact on the improvement of the quality of life. It is this particular area of chemical science, where major changes have taken place, leading to the development of innovative processes and cleaner technologies. It is now well understood that processes involving catalysts not only allow better means to achieve high selectivity for a desired product, but also provide cleaner technologies, unlike the conventional processes which may pose serious waste disposal problems^{1,2}. The focus in earlier days was narrowed down to the final product and its quality, while accepting poor overall yields in many cases, unlike the present day situation where increasing competition and stringent environmental regulations have led to the development of new catalytic processes and catalysts which can prove not only economical but also provide eco-friendly technologies. Today, a variety of organic transformations are carried out using both homogeneous and heterogeneous catalysts. It is now well established that transition metals like Pd, Pt, Ru, Rh, Co and especially Ni can catalyze such transformations. For a commercial process, it is often desirable to have a cheaper catalyst with high activity and selectivity. In this context, both homogeneous and heterogeneous Ni catalysts are highly promising considering the economics of the process industry. This paper aims to review some

important industrial applications of homogeneous and heterogeneous Ni catalysts.

The homogeneous and heterogeneous Ni catalysts have found wider applications in the chemical process industry ever since the use of catalysts for commercial purposes was exploited. In fact, it is one of the oldest catalysts³. The metal nickel (meaning bad boy in German) was isolated in pure form by Cronstedt in 1754. The first carbonyl Ni complex, $[\text{Ni}(\text{CO})_4]$, was discovered by Mond in 1888, and this initiated development of organonickel chemistry. Nickel is the only metal that can form complexes of the type $[\text{Ni}(\text{CO})_4]$ at room temperature and can dissociate into CO and Ni metal at slightly higher temperatures. This procedure is followed even today to obtain pure metallic Ni. The substitution of carbonyl groups in $[\text{Ni}(\text{CO})_4]$ by other electron donor ligands such as phosphines, isocyanides, pyridyl type ligands forms the basis for the preparation of an extensive series of related $d^{10} \text{Ni}^0$ organometallic complexes³. The development of homogeneous Ni catalysis was mainly initiated by Reppe and Wilke², who synthesized a series of organo-Ni complexes for such reactions as carbonylation and polymerization, commonly used in chemical industry even today. The discovery by Holzkamp in 1952, that Ni salts can alter the AlR_3 (where R represents alkyl group) catalyzed growth reaction of ethylene to α -olefins in such a way as only dimers are formed, is a phenomenon referred to as "Nickel Effect", and is considered to be

important as it led to the invention of "Ziegler Catalysis", which is a common reaction in industry for the production of a variety of polymers and also has a strong academic potential. Many important carbon-carbon bond formation reactions such as carbonylations, cyclic and linear oligomerizations and polymerizations of monoenes and dienes are carried out using organo-Ni complex catalysts to achieve high selectivity. These reactions are discussed along with their applications and some novel organo-Ni catalysts for potential reactions in this article.

If Reppe and Wilke were responsible for the vast development of homogeneous catalysis with Ni complex catalysts, it was Sabatier who in 1906 reported the hydrogenation of carbon monoxide to methane using heterogeneous Ni catalysts. In fact, one of the oldest hydrogenation catalyst is Raney-Ni which was first used industrially in 1925, but due to its pyrophoric properties, was found unsuitable for many catalytic processes. Heterogeneous Ni catalysts are commonly used in chemical process industry in a variety of hydrogenation reactions. In this context, supported Ni catalysts, in which the active Ni metal is dispersed on a large surface area of an inorganic material such as Al_2O_3 , SiO_2 and zeolites, have received much attention, as many inherent drawbacks of unsupported Ni catalysts can be avoided. Also, a variety of bimetallic Ni catalysts, supported and unsupported, exists today which find commercial applications mainly for different hydrogenation processes. Some of the industrially important reactions carried out with homogeneous and heterogeneous Ni catalysts are :

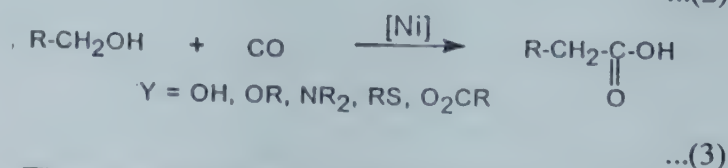
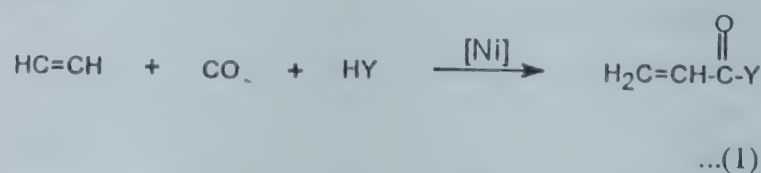
- Hydrogenation of oils
- Hydrogenation of aromatics
- Hydrogenation of carbonyl group containing organic compounds
- Hydrogenation of nitro group containing organic compounds
- Hydrogenation of carbon-carbon double and triple bonds
- Hydrogenation of nitrile group containing organic compounds
- Carbonylation of alcohols
- Carbonylation of esters
- Carbon-carbon coupling reactions
- Oligomerization of olefins
- Dimerization of olefins

- Cyclization of olefins
- Isomerization of olefins
- Polymerization of olefins
- Hydrocyanation of olefins
- Teleomerization of olefins

This paper summarizes the applications of homogeneous and heterogeneous Ni catalysts. The use of a zeolite supported Ni catalyst for some industrially relevant hydrogenation reactions is also described. Finally, some potential areas for research such as enantioselective hydrogenation using chiral modifiers have also been covered to give a better impact of the vast application of Ni catalysts.

Homogeneous Ni Catalysts

Reppe discovered a series of homogeneous catalytic reactions catalyzed by $\text{Ni}(\text{CO})_4$ and called them as carbonylation reactions, while searching alternate applications of carbon monoxide produced as a byproduct in the manufacture of acetylene⁴⁻⁷. This heralded the beginning of the development of homogeneous Ni catalysts, some fifty years ago. The series of reactions which Reppe called as carbonylations are :



These reactions are considered important in industrial catalysis; however, some of these reactions today involve novel organo Rh, Ir and Co complexes as catalysts along with Ni complex catalysts⁸⁻¹⁰. Carbonylation of alcohols to acids, esters to anhydrides and olefins to acids are some of the important industrial reactions used in the production of a variety of fine chemicals, pharmaceuticals, petrochemicals, food preservatives, insecticides and agrochemicals. Examples of some specific carbonylation reactions are :

- Carbonylation of methanol to acetic acid

- Carbonylation of ethanol to propionic acid
- Carbonylation of propanol to butyric acid
- Carbonylation of methyl acetate to acetic anhydride.

In these reactions, the carbonylation of methanol to acetic acid is the most widely used industrial process, acetic acid being the building block for the synthesis of a variety of speciality products and pharmaceuticals. Some important homogeneous Ni catalysts used for carbonylation of alcohols are : $\text{Ni}(\text{CO})_4$, NiI_2 , NiCl_2 , $\text{Ni}(\text{NH}_3)_6\text{Cl}_2$, $\text{NiCl}_2(\text{PPh}_3)_2$, $\text{Ni}(\text{acac})_2$, $\text{Ni}(\text{OAc})_2$, $\text{Ni}(\text{propionate})_2$ and $\text{Ni}(\text{isoquinoline})_4\text{Cl}_2$ ¹¹⁻¹³. The preparation of these complexes has been well documented¹⁴⁻¹⁶. It has been reported that metal iodides can be used as promoters for carbonylation instead of HI as it is corrosive. A number of patents report the carbonylation of methanol to acetic acid using homogeneous Ni catalysts at low temperatures and pressures¹¹⁻¹³. A Ni-isoquinoline complex, $[\text{Ni}(\text{isoq})_4\text{Cl}_2]$, has been found to be highly effective for carbonylation of alcohols. The patents indicate that using such a complex along with metal iodides as promoters, high conversions of alcohols (>98%) with selectivity as high as 96% to the desired acids can be obtained. Carbonylation of methanol, ethanol, propanol and methyl acetate has been studied using this catalyst¹⁷⁻²⁰. It offered not only a higher alcohol conversion but also high selectivity towards the desired acid. One more important outcome of this work was the use of this catalyst at low partial pressures of carbon monoxide without much affecting the selectivity towards the desired acid, thereby reducing the investment cost on high pressure equipment. More importantly, it provides a cheaper alternative catalyst for expensive organo-Rh complexes for carbonylation of alcohols. A comparison of the performance of different types of homogeneous organometallic catalysts is shown in Table 1. The study reveals that Rh catalysts (Monsanto's process) are the best except for the economics of the overall process. However, these aspects have been well worked out for any industrial plant and one can hope that Ni catalysts can become a better choice.

The mechanism of carbonylation of alcohols using Ni complex catalysts is well documented. Heck²¹ proposed a mechanism (see Fig. 1) in which the active catalytic species involved was $\text{Ni}(\text{CO})_4$. Oxidative addition of alkyl iodide to this species gives

Table 1 — A comparison of different catalysts for carbonylation of methanol²⁰

Catalyst	Pressure MPa	Temperature K	Selectivity to acetic acid, %
Co	7-70	350-530	90
Ni (unmodified)	4-30	423-500	70-75
Ni	3-5	423-473	80-90
Ni (isoq)	0.5-5	478-508	>97
Rh	0.1-1.5	423-473	100

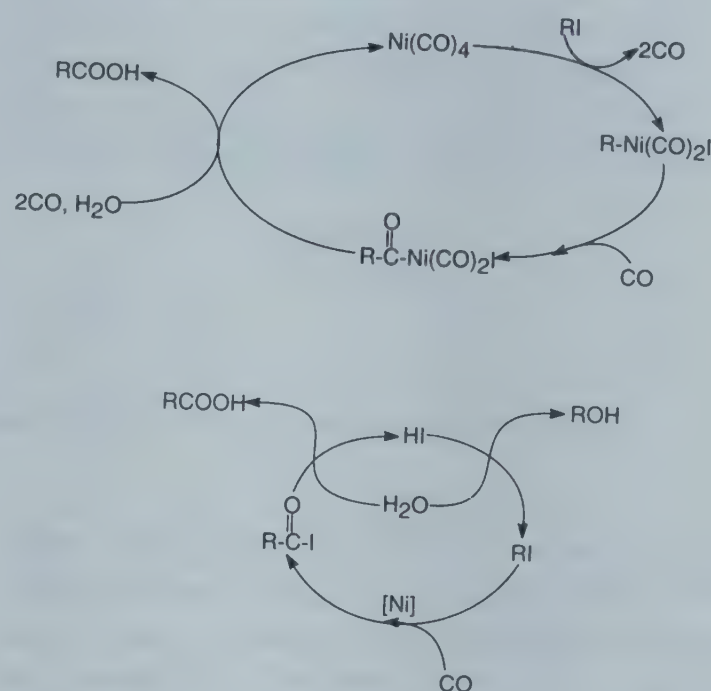


Fig. 1 — Mechanism of Ni-catalyzed carbonylation of alcohols²¹

an intermediate catalytic species of the form $\text{R-Ni}(\text{CO})_2\text{I}$ to form an acetyl iodide complex which on high concentrations of iodine is eliminated and it reacts with water to produce acetic acid.

Another important area of application of organo-Ni complex catalysts comes from the pioneering contributions of Wilke in the 1960's. A mixture of $\text{NiCl}_2/\text{Et}_2\text{AlCl}$ and butadiene resulted only in polybutadiene (discovery of Ziegler catalysis), while, Wilke demonstrated that a combination of Ni-acetylacetonate and AlEt_2OEt could produce a variety of products by control of oligomerization of butadiene by ligands of the type R_3P (where R represents an alkyl group). A wide range of useful products (linear and cyclic compounds) are reported during butadiene

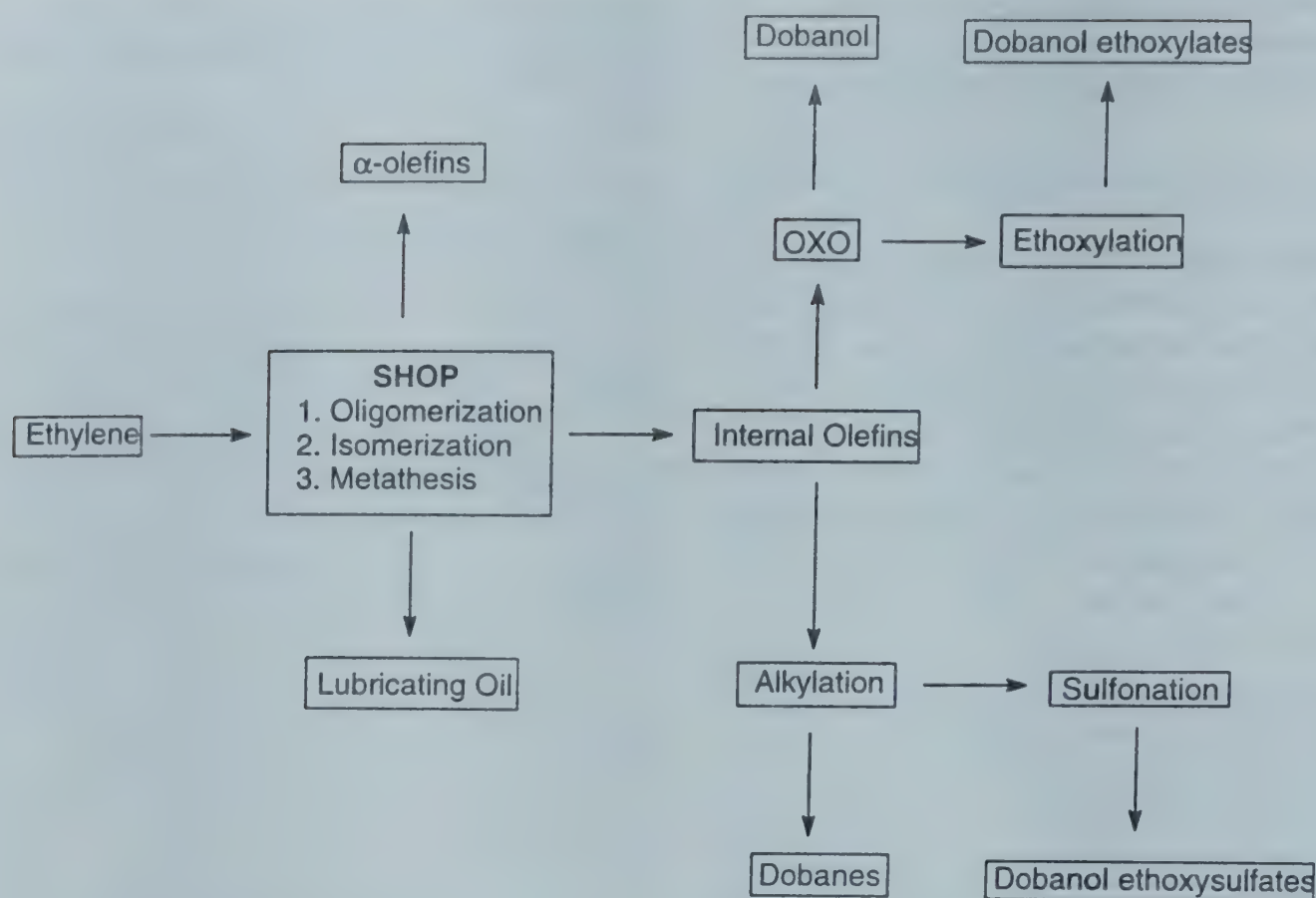


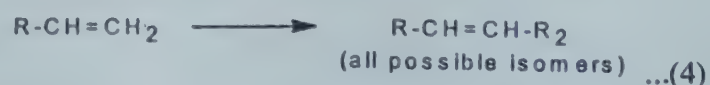
Fig. 2 — Products of Shell higher olefin process²⁴ (Dobane derivatives are trade names of Shell for detergents)

oligomerization by suitably "tailoring" the catalyst with the help of different ligands. Some important products formed are cyclododecatriene and cyclooctadiene. Cyclododecatriene finds application in the manufacture of Nylon-12 derivatives, as practiced by Huls AG (18,000 tonnes per year) and Dupont²², while, cyclooctadiene is used in the manufacture of olefins by Feast Process²³. Homogeneous Ni catalysts are extensively used in converting ethylene to α -olefins — a process developed by Shell Oil company²⁴. The success of this process lies in the flexibility to produce a wide variety of high quality olefins which are used in detergents. This process is also known as Shell Higher Olefin Process (SHOP).

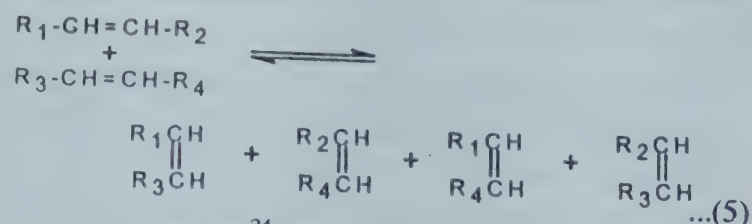
Among the other advantages of this process over the existing alternatives are its lower cost and reduced environmental effect. This process was considered to be one of the largest applications of homogeneous catalysis, especially Ni with approximately one million tonne capacity in 1990. A block diagram of this process is shown in Fig. 2. Ethylene oligomers are produced which are up to 99% linear, of which 98% are α -olefins. The remaining unmar-

ketable α -olefins are isomerized and converted a three step metathesis reaction into linear olefins with internal double bonds. The reactions involved are isomerization and disproportionation.

Isomerization:



Disproportionation:



It was reported²⁴ that more than 99% mono-olefins and 94-97% normal olefins can be obtained along with paraffins, conjugated dienes, aromatics, etc.

Other potentially important reactions using homogeneous Ni catalysts are : hydrocyanation of mono- and di-olefins, teleomerization and the famous Heck reaction which is a carbon- carbon coupling reaction.

Heterogeneous Ni Catalysts

One of the most important reaction using heterogeneous Ni catalysts is the hydrogenation of vegetable fats. Though several other reactions such as carbonylation, reductive amination, oxidation, carbon-carbon coupling, etc. have been reported using supported Ni catalysts, none has reached the stage of commercialization. Today, hydrogenation of organic compounds containing carbon-carbon double and triple bonds, carbonyl groups, nitro groups, nitrile groups, etc. are carried out using H_2 (gas) and supported Ni catalyst in a suitable solvent. Liquid phase catalytic hydrogenation for the synthesis of fine chemicals and pharmaceuticals is a major recent development. It has replaced the conventional synthetic routes of using stoichiometric reducing agents like Fe/HCl , which pose serious environmental prob-

lems. Also, high yields of the final desired products can be obtained through selective hydrogenation by tailoring the catalyst and the reaction conditions. These catalytic routes are widely acceptable in industries considering the economics as well as the environmental issues. The end products usually find applications in fine chemicals and pharmaceuticals. For example, the hydrogenation of *p*-isobutyl acetophenone to *p*-isobutyl phenyl ethanol is carried out using Ni-catalysts besides Pd and Rh supported catalysts. This reaction has industrial importance as *p*-isobutyl phenyl ethanol is an intermediate in the manufacture of Ibuprofen, a non-steroidal anti-inflammatory drug considering the new catalytic route developed for Ibuprofen by Hoechst-Celanese and Boots as shown in Fig. 3¹. This route not only reduces the number of reaction steps but also the byproduct

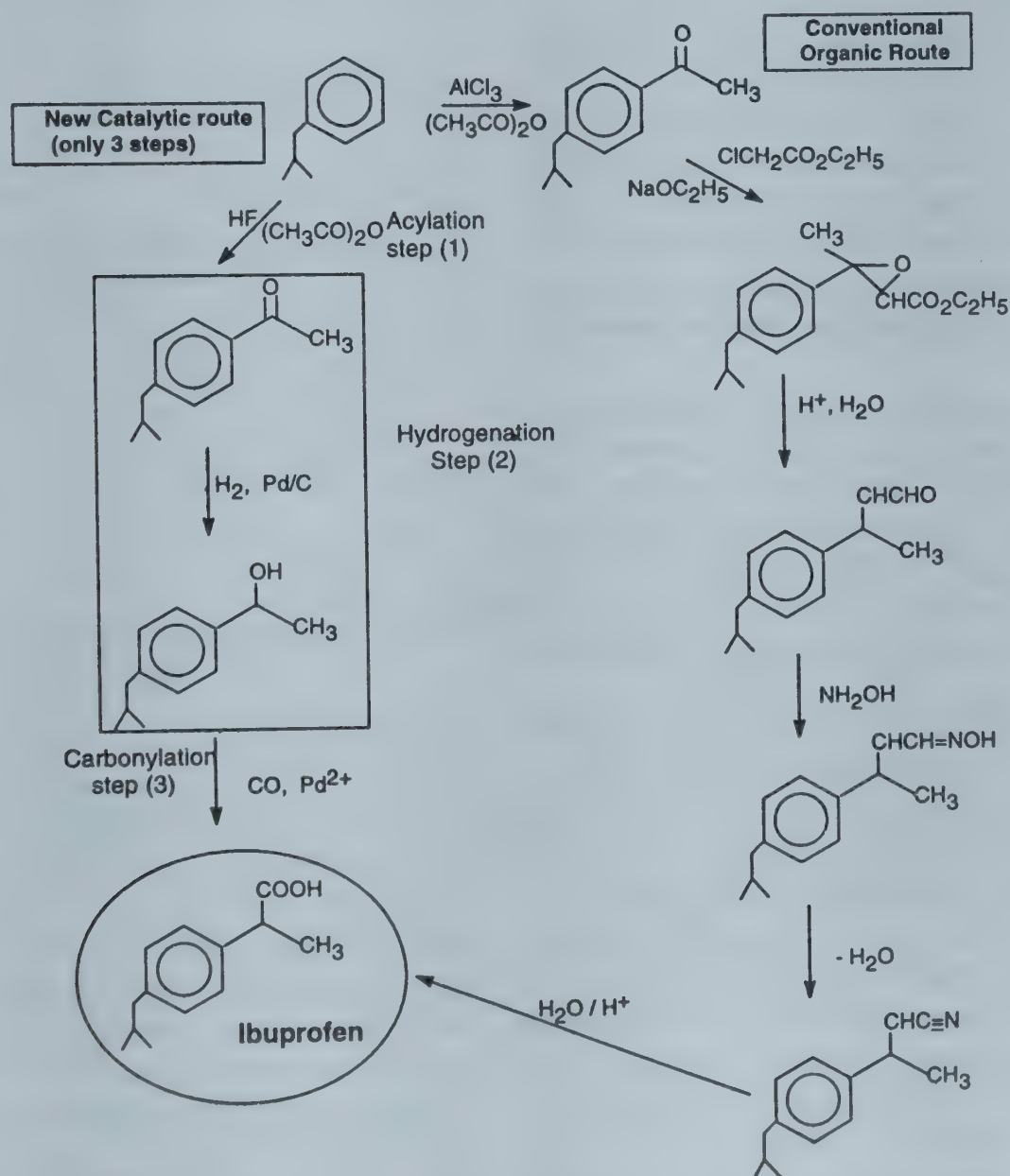


Fig. 3 — Conventional organic and new catalytic routes for Ibuprofen production¹

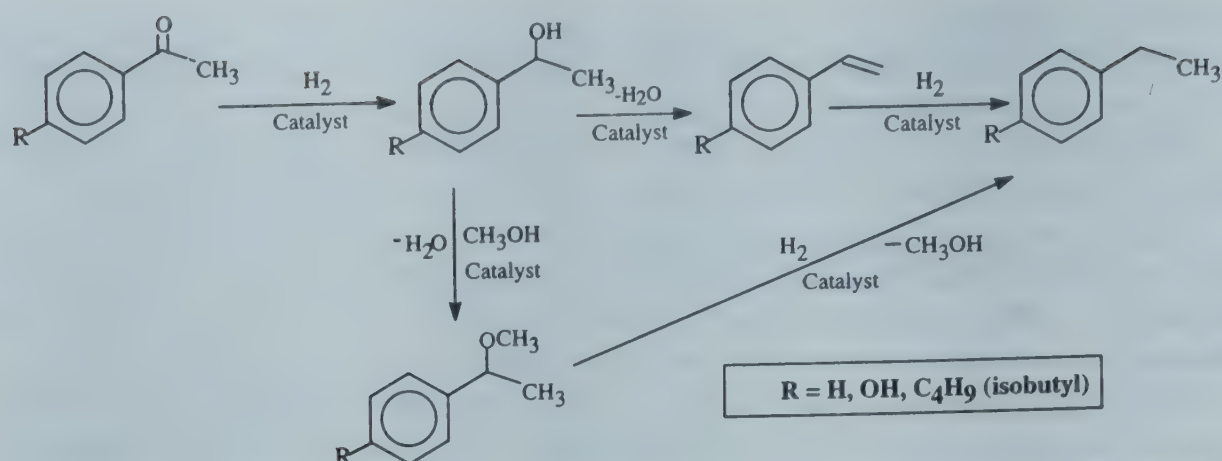


Fig. 4 — Reaction scheme for hydrogenation of substituted acetophenone derivatives²⁶⁻²⁸

formation, if compared to the conventional synthetic route. In fact, researchers are trying to replace the corrosive HF acylation (step 1) in this process by environmentally benign potential acid catalysts such as zeolites, clays and solid super acids, etc. and if this is achieved, it can be a major breakthrough in processes of this type. The primary motivation for such novel technologies has been the stringent HF regulation in countries like USA. A number of reports reflect the application of zeolites and catalysts such as scandium triflate in such acylation reactions but these have not yet reached the stage of commercial application²⁵.

Hydrogenation of acetophenone derivatives is important in the synthesis of a variety of pharmaceutical products. Recently, it has been shown that these reactions can be carried out effectively using supported Ni catalysts²⁶⁻²⁸. These authors have studied the kinetics of these reactions and have also proposed rate models²⁶⁻²⁸. Based on the product identification and distribution, they have proposed the reaction scheme as shown in Fig. 4. A typical concentration-time profile for hydrogenation of *p*-isobutyl acetophenone is shown in Fig. 5. It can be observed that the ether derivative formed due to interactions of the support with the intermediate products and the solvent used, altered the selectivity-pattern towards the desired product. One important aspect involved in hydrogenation of such organic compounds containing carbonyl groups is selective reduction of the carbonyl group to its corresponding secondary alcohol. This was achieved by making the reaction medium alkaline. Chart 1 shows some interesting results about the improved selectivity (selectivities as high

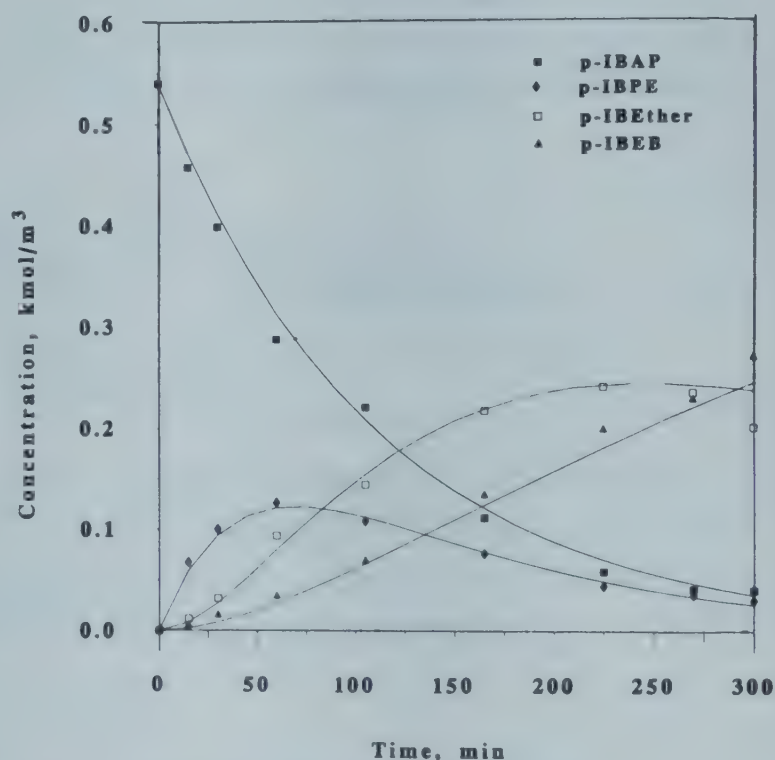


Fig. 5 — Concentration - time profile for hydrogenation of *p*-isobutyl acetophenone at 393 K²⁶⁻²⁸

as 99% can be achieved) towards the secondary alcohol derivative (desired product) for various substrates investigated. Interestingly, it was observed that the addition of alkali only promotes the selectivity without much altering the conversion of the substrate, keeping all other parameters constant as the conversion levels for these substrates were found to be the slightly higher (not more than 10%) when the reaction was carried out in the absence of alkali²⁶⁻²⁸.

Hydrogenation of 2,4-dinitrotoluene (DNT) using supported Ni-catalysts to produce 2,4-toluene diamine (TDA) which finds application in the manufacture of toluene diisocyanate (TDI) is another im-

portant reaction^{29,30}. Toluene diisocyanate is an important intermediate in the manufacture of polyurethane foams and certain polyamides. The worldwide production of TDI in 1991 was around 7 million tonnes^{29,30}. The overall reaction mechanism was ex-

plained in many cases by the well known Haber's reduction mechanism of nitro compounds. Hydrogenation of DNT proceeds via formation of two stable mono nitro intermediates, viz. 2-amino-4-nitro toluene (2A4NT) and 4-amino-2-nitro toluene (4A2NT) to the final hydrogenated product TDA, as shown in Fig. 6. In some cases, 4-hydroxylamino-2-nitro toluene was also detected (see Fig. 6). Due to the high exothermic nature of the reaction ($-\Delta H = 556$ kJ/mol of nitro group³¹) and temperature sensitive DNT (can prove to be an explosive at temperatures above 120°C), the reaction is usually carried out at mild conditions of temperature and pressure in either mechanically agitated pressure reactors or fixed bed catalytic reactors. Several commercial processes exist in which DNT is suitably hydrogenated to TDA under a wide range of operating conditions. In this context, activated Ni, supported Ni and Raney Ni as catalysts have also been found to be suitable, even though supported Pd catalysts are widely used for hydrogenation of DNT to TDA. One of the most important commercial processes for hydrogenation of DNT is the Bayer/Mobay process in which activated Ni catalyst is used²⁸.

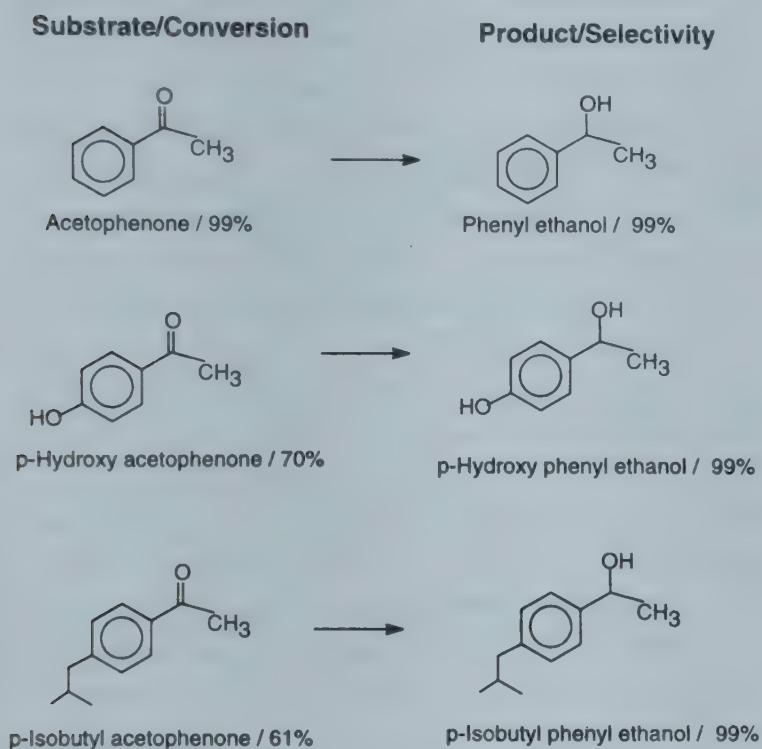


Chart 1 — Improved selectivity aspects in hydrogenation using supported Ni catalysts²⁶⁻²⁸

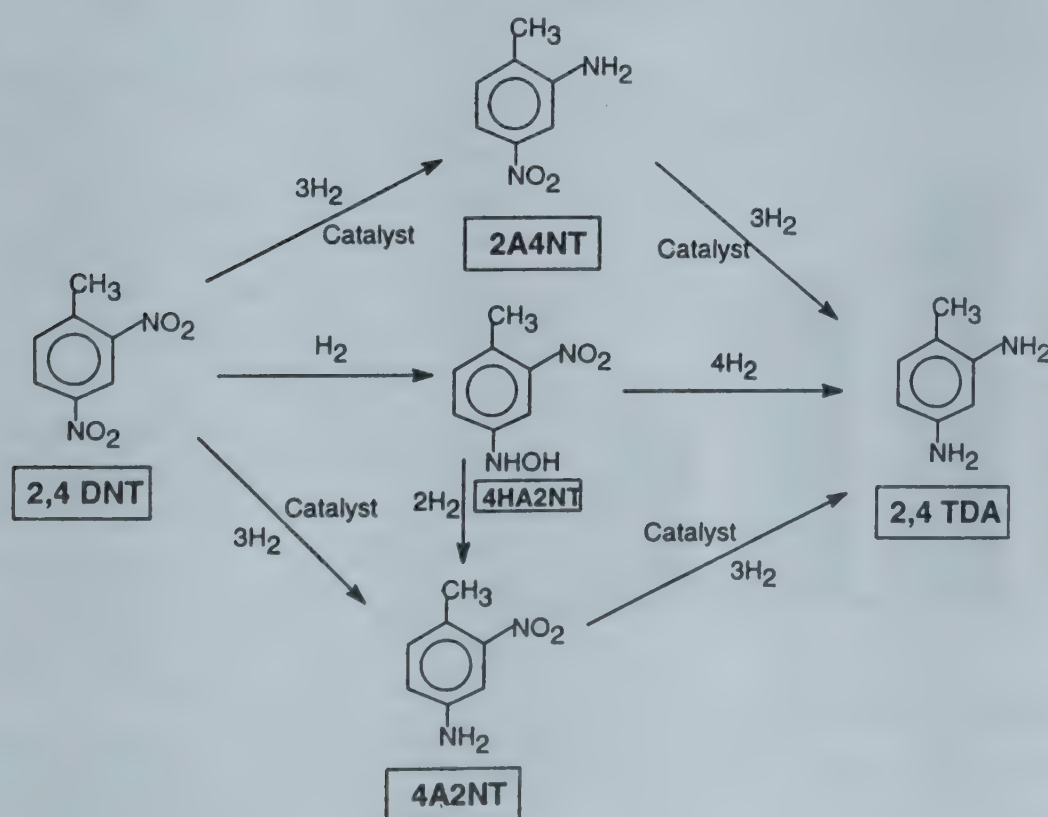


Fig. 6 — Reaction scheme for hydrogenation of 2,4 -DNT²⁸

The kinetics of hydrogenation of DNT to TDA using a Ni-supported catalyst has been reported recently^{28,34}. These authors have investigated the kinetics and intraparticle diffusion effects in a semi-batch slurry and basket type reactors. The reaction scheme is well represented as shown in Fig. 6. A similar type of reaction scheme was also found to be representative for supported Pd catalysts. The products formed during hydrogenation were similar using either supported Pd or Ni catalysts. The performance comparison of supported Pd and Ni catalysts in terms of conversion of DNT and selectivity towards TDA is shown in Fig. 7. As evident from this figure, the supported Ni catalysts are highly promising (especially 20%Ni/HY) and can be used as an alternative for Pd based catalysts, which are highly expensive. A plot of concentration vs time of different reactants/products indicated that the 4A2NT intermediate was formed in excess as compared to 2A4NT. After three hours of reaction, the selectivity towards TDA was >90%.

The above mentioned examples (hydrogenation of *p*-isobutyl acetophenone and DNT) clearly indicate the robustness of supported Ni catalysts in complex exothermic reactions and thus, indicate that these catalysts have potential of being used in heterogeneously catalysed organic transformations.

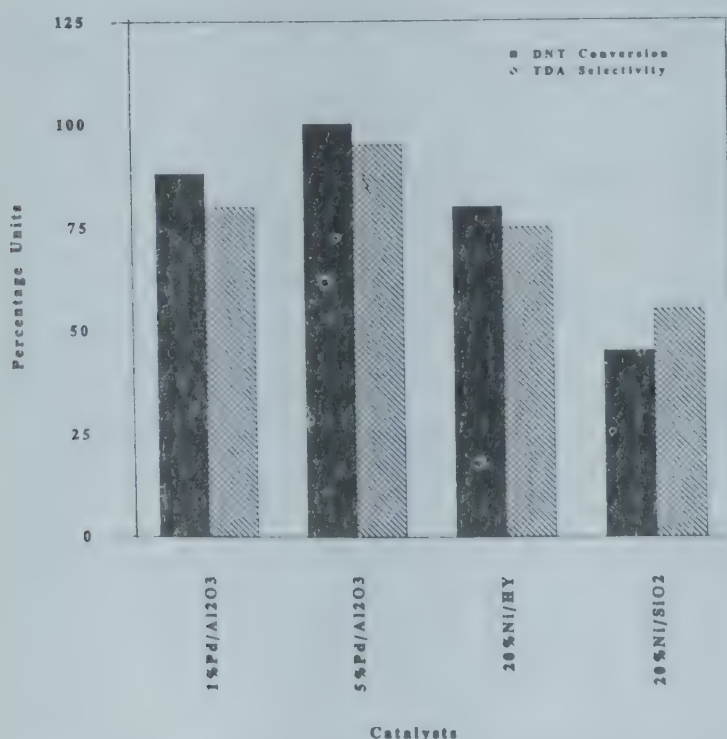


Fig. 7 — A performance comparison of supported Pd and Ni catalysts^{28,32,33}

Enantioselective Hydrogenation Using Heterogeneous Ni Catalysts

Enantioselective synthesis of organic compounds such as β -keto esters and carbonyl group, finds applications in the area of pharmaceuticals and fine chemicals. Research in this field is being conducted to develop better catalyst systems and several reviews have discussed the key aspects involved³⁵⁻³⁹. In these cases, the solid catalyst is modified by the addition of chiral molecules in a manner that the substrate molecule gets hydrogenated preferentially from one direction, leading to the enantiomeric excess (*ee*) of the product. Recent reports indicate the use of heterogeneous Ni catalysts (Raney Ni as well as supported Ni catalysts) modified by chiral auxiliaries, in some cases along with NaBr (to improve the optical yields [%*ee*]) in enantioselective hydrogenation. Supported Pt and Pd catalysts have also been reported to be equally useful in enantioselective hydrogenations. In Chart 2, typical chiral auxiliaries are summarized. Some important enantioselective hydrogenation reactions carried out by modified Ni catalysts include:

(a) Hydrogenation of methyl-2-methyl-3-oxobutyrates: Tartaric acid modified Ni is used to produce the hydrogenated product which is an intermediate for the sex pheromone of the pine sawfly (see Fig. 8a).

(b) Hydrogenation of acetylacetone: This is carried out using tartaric acid modified Raney Ni catalyst in the presence of NaBr. The product finds application in a variety of ligand synthesis used in homogeneous catalysis (see Fig. 8b).

(c) Hydrogenation of methyl acetoacetate using Ni/SiO₂ catalysts modified by tartaric acid or amino acids.

(d) Hydrogenation of β -keto ester, shown in Fig. 8c, is carried out using tartaric acid modified Raney Ni catalyst and finds application in the synthesis of tetrahydrolipostatin, a pancreatic lipase inhibitor developed by Hoffmann-La Roche. The results indicate that 90-92% *ee* is obtained at 6-100 kg reaction scale with 100% chemical yield^{36,37}.

(e) Hydrogenation of acetophenone using supported Ni catalyst modified by S-proline.

In most of the above examples, enantioselective hydrogenations using tartaric acid modified Ni catalysts have been reported³⁵⁻³⁹. In fact, this catalyst is

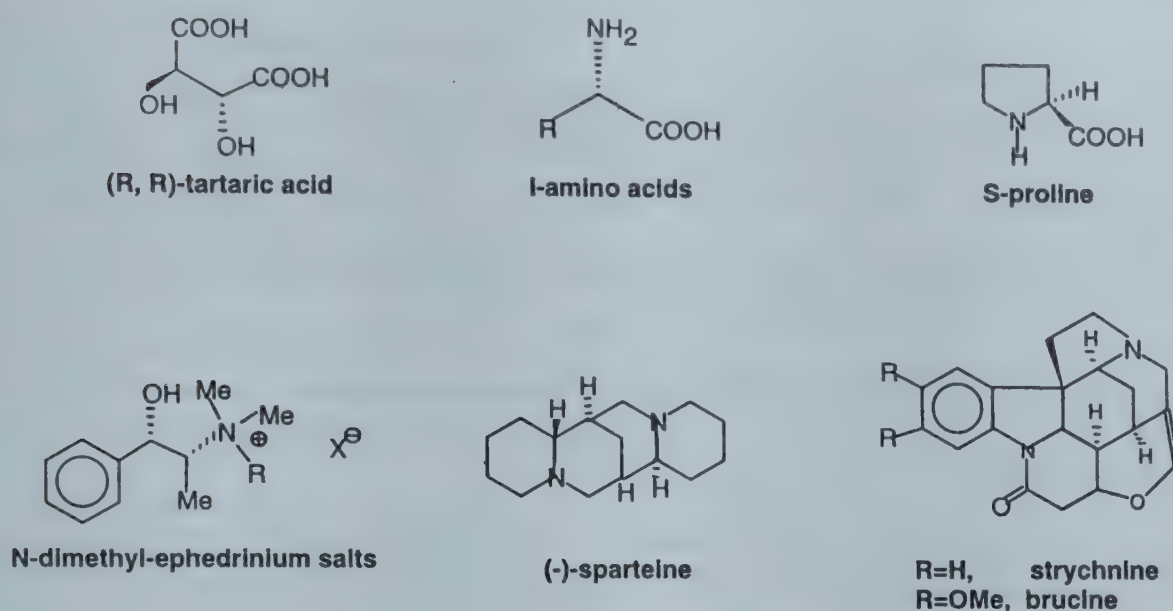


Chart 2 — Some important chiral auxiliaries

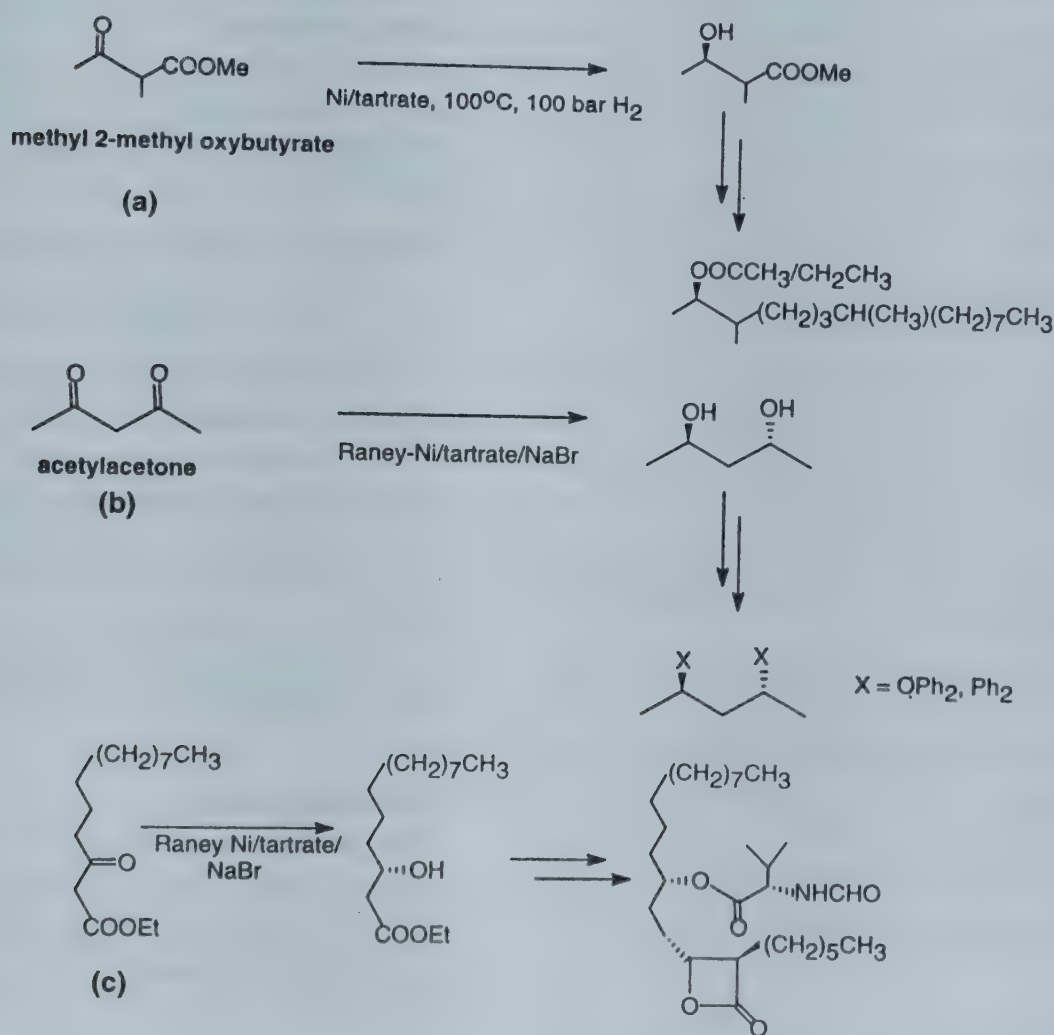


Fig. 8 — Some examples of enantioselective hydrogenations³⁹

now commercially available with M/s Degussa. Understanding the mechanism of action of these catalysts is certainly a challenge. It is clear that along with the process parameters and catalyst preparation

methods, the effect of modifier concentration, chemistry of the modifier, pH of the modifier concentration (as the catalysts are first subjected to solutions of chiral modifiers and then used for hydrogenation

$\begin{array}{c} \text{COOH} \\ \text{CH}_3 \\ \text{H} \\ \text{COOH} \end{array}$	$\longleftrightarrow$	$\begin{array}{c} \text{COOH} \\ \\ \text{H}-\text{C}-\text{OH} \\ \\ \text{H}-\text{C}-\text{OH} \\ \\ \text{COOH} \end{array}$	$\longrightarrow$	$\begin{array}{c} \text{COOH} \\ \text{OCOPh} \\ \text{OH} \\ \text{COOH} \end{array}$	$\begin{array}{c} \text{COOH} \\ \text{OMe} \\ \text{OH} \\ \text{COOH} \end{array}$	$\begin{array}{c} \text{COOH} \\ \text{H} \\ \text{OH} \\ \text{COOH} \end{array}$	$\begin{array}{c} \text{COOH} \\ \text{OMe} \\ \text{OMe} \\ \text{COOH} \end{array}$	$\begin{array}{c} \text{CH}_3 \\ \text{OH} \\ \text{OH} \\ \text{COOH} \end{array}$
(%ee)	75	83	65	68	61	0.2	1.2	

Fig. 9

tions), adsorption of the modifier and substrate need to be considered. Some of these aspects have been reviewed earlier³⁵⁻³⁹. The studies indicate that structural effects often play an important role in the enantioselective hydrogenation. For example, while using tartaric acid modified Ni catalysts for β -ketoester hydrogenation reactions (see Fig. 8), at least two carboxyl and one -OH groups are essential in order to get reasonable enantioselectivities (% ee). The change in % ee with changes in substituent group in the chiral modifier (i.e. tartaric acid) during a β -ketoester hydrogenation is shown in Fig. 9.

Also, under optimized conditions a corrosive modification of the Ni surface occurs and it has been hypothesized that the tartrate molecule is chemically bonded to Ni via two carbonyl groups and during hydrogenation, the adsorbed tartrate does not leave the surface, thereby allowing the substrate molecule to get hydrogenated only in one particular direction by interacting with it.

Thus, these reactions, catalyzed by chiral solids, are useful from synthetic point of view. However, compared to chiral homogeneous and bio-catalysis, the enantioselectivities are usually lower. From a technical or commercial point of view, these catalysts would be preferable to homogeneous catalysts because of ease in handling and separation.

Concluding Remarks

In this article, some industrial applications of homogeneous and heterogeneous Ni catalysts has been reported. The homogeneous Ni catalysts have been extensively used for carbonylation of alcohols and acetates to produce corresponding acids and anhydrides and for oligomerization, polymerization of olefines. The heterogeneous Ni catalysts (or more specifically the Ni-supported catalysts) are used in a

variety of hydrogenation reactions. Hydrogenation of DNT and acetophenone derivatives are discussed in this article as specific examples. A comparison of the performance of Ni and Pd based catalysts for hydrogenation of DNT has shown that the former are highly promising for commercial applications particularly from economic point of view. The application of heterogeneous Ni catalysts by suitably modifying the catalysts using chiral modifying agents such as tartaric acid etc. for enantioselective hydrogenation of β -keto esters has been discussed.

A number of organo-Ni complex catalysts are being studied for commercial exploitation of some key carbonylation reactions of aryl halides and aromatic alcohols to produce corresponding acids. The use of heterogeneous Ni catalysts is increasing especially for selective hydrogenation of organic compounds with various functional groups. However, the main problem associated with heterogeneous Ni catalysts is its deactivation. In this context, the use of bimetallic catalysts is gaining significance and needs a detailed study.

Acknowledgement

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Assessment of Demand and Supply of Alcohol for Fuel Purpose with Special Reference to UP

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The feasibility of the proposal by distillers that surplus alcohol could be utilized as a blending agent or an oxygenator in gasoline for replacement of motor spirit has been examined in detail in the light of availability and quantum of surplus alcohol in the case of Uttar Pradesh. From the technical evaluation, energy analysis and availability of surplus refining capacity presented in the study, it is suggested that the best viable alternative for UP in the event of having any surplus alcohol, if any, is to maintain at least 20 per cent of its total traditional requirements as a buffer stock and remaining surplus, if any, could be exported rather than using it for fuel blend or oxygenator.

There has been a move by the owners of distilleries to impress upon the government that surplus alcohol could be utilized as a blending agent or an oxygenator in the gasoline and thus could serve as a part or full replacement for motor spirit (petrol and diesel). In this paper a study of the proposal from the point of view of availability and quantum of surplus alcohol, if any, in the state of Uttar Pradesh has been reported.

Alcohol Availability

Requirement of Alcohol for Fuel Programme

Motor spirit (fuel) essentially comprises petrol and diesel and its statewide consumption for the past 5 years is presented in Annexure I. From this, it can be inferred that UP's requirement of motor spirit works out to roughly about 10% for petrol and 14% for high speed diesel oil (HSDO) of the total all India requirement and UP happens to be the state with the highest HSDO consumption. On an average about 82% of the HSDO is utilized in the transport sector and this basis has been taken to project the requirement of petrol and diesel in UP till 2000 AD.

A minimum of 10% ethanol (ethyl alcohol) blending for petrol and 15% ethanol blending for diesel has been considered by the Indian Institute of Petroleum(IIP), Dehradun for working out the alcohol requirement for use in blending with fuel in road transport (Annexure II). Assuming the historical compounded growth rate of 2.15% in case of petrol and 8.60% in case of diesel, the yearwise projection of alcohol requirement for transport fuel in UP is presented in Annexure III. On a cumulative basis the total alcohol requirement for part replacement of fuel in the transport sector ranges from 5582.87 lakh litres in 1995-96 to 76511.11 lakh litres by 2000 AD.

For octane enhancement and oxygenation ethanol has to be blended at 10% v/v which implies that the ethanol requirement for oxygenators in the state would be between 5304 lakh litres in 1995-96 and 7269 lakh litres by 2000 AD. Such huge quantity of alcohol is not available in the state as explained earlier.

Availability of Surplus alcohol

Alcohol Production

From the realistic trend analysis as presented to the state earlier, the molasses production is expected to range from 225 lakh quintals in 1995-96 to 242.74

Table 1 — Expected alcohol consumption during 1995-2000

Year	Chemicals and others	Potable units	Exports to states*	New Units	Unit: Lakh litres
					Total State demand
1995-96	1750.38	1152.28	257.44		3160.10
1996-97	1951.73	1325.12	283.19		3560.04
1997-98	2176.79	1523.89	311.51	652.40	4664.58
1998-99	2428.41	1752.47	342.66	978.59	5502.13
1999-2000	2709.74	2015.34	376.92	1630.99	6732.99

*Alcohol requirement of neighbouring alcohol deficit states to whom UP has traditionally been supplying alcohol

lakh quintals by 2000 AD. Going by the trend exhibited in the state it is only about 85% of the total molasses production which is distilled while the remaining quantity is utilized by cattlefeed manufacturers and other direct molasses users. On this basis it can be projected that the likely alcohol production in the state would be about 4399 lakh litres in 1995-96 and 4746 lakh litres by 2000 AD.

Alcohol Consumption

The historical annual compounded growth rate in alcohol consumption by the chemical sector has been 12% while in case of potable sector it has been around 15%. The state has also granted alcohol assurances for new projects (Annexure IV) to the tune of about 1630.99 lakh litres and it is expected that at least 40% of these assurances will mature by 1997-98 while the rest shall mature over the subsequent years by 2000 AD. On the above assumptions, the expected alcohol consumption within the state (not considering expansions being planned and proposed by the existing alcohol based chemical units on the basis of their FL39 licensed capacity) is shown in Table 1.

Surplus Alcohol

The alcohol requirement for traditional sectors (chemical and others and potable) and the fuel sector vis-a-vis the likely availability is presented in Table 2.

From Table 2, it can be concluded that alcohol available within the state can never take care of the cumulative demand of even the traditional sectors leave apart the minimum alcohol requirement for any fuel programme. The meagre surplus in the first two years of projection can cater to only an insignificant percentage of the alcohol for fuel requirement of the state in the corresponding years. In the later years,

Table 2 — Alcohol requirement during 1995-2000

Year	Total availability (lakh ltrs)	Total requirement* (lakh ltrs)	Surplus for fuel (lakh ltrs)
1995-96	4398.75	3160.10	1238.65
1996-97	4151.05	3560.04	591.01
1997-98	4363.95	4664.58	-300.63
1998-99	4588.19	5502.13	-913.94
1999-2000	4745.57	6732.99	-1987.42

*Requirement of the traditional sectors which includes chemicals and new projects, potable and export to neighbouring alcohol deficit states.

however, there is no surplus but a deficit as the alcohol availability will be far less than the requirement of alcohol for the traditional use of industrial chemicals and potable liquor. Taking into consideration the minimum requirement of alcohol to sustain a meaningful fuel programme in the state, the overall molasses requirement in the state would have to be between 377 lakh quintals in 1995-96 and 623 lakh quintals in 2000 AD, which is difficult to achieve.

Technical Constraints

As a Blend

Salient features of a fleet trial aimed at studying the fuel economy and drivability in case of ethanol blended fuel conducted by IIP and IOC (R&D) are:

Under city driving, fuel economy loss was 1% with 10% ethanol blended fuel (E10) and 3.90% with 20% ethanol blended fuel (E20). Under highway driving the fuel economy loss was 3.5% in case of E10 and 4.3% for E20.

Hot startability and drivability demerits have been found higher with blends specially in Ambassador and Standard cars.

Wear of cylinder bore and ring was higher with E20 relative to petrol.

Low octane number and high self ignition temperature makes alcohol unsuitable for diesel engines unless the fuel or the engine is modified to match the other.

Alcohol and diesel are not miscible with each other and thus cannot be used as blends.

Calculation of the pay back period on conversion of buses/trucks show that diesel cost at present (Rs 8.50/l) is lower than the alcohol cost and alcohol operation in terms of Rs/Km is not economical.

In gasoline 100% anhydrous alcohol (neat alcohol) would be preferred in the long run which would make the use of blended fuel more uneconomical.

A long term continued availability of alcohol will be required to come up with any meaningful alco-fuel programme and it has to be fully commercialized to gain economical advantage which would require large commercial scale experimentation with alco-fuel which has not so far been conducted.

As an Oxygenator

The various aspects of oxygenators are:

Road traffic is a major source of pollution and produces substantial percentage of nitrogen oxides (NO_x), hydrocarbons and carbon monoxide. Today practically all new cars are equipped with catalytic converters which are very efficient being capable of reducing the above pollutants by more than 90% in ideal conditions and subsequent emissions are well within the statutory limits.

Fuel quantity (in terms of low emission levels of regulated, toxic and ozone forming exhaust components) can be enhanced by the use of oxygenates also. Oxygenates are the oxygen-containing compounds which boost up the knock resistance and improve the combustion quality. The use of alcohols (ethyl alcohol) as oxygenates would surely improve the fuel octane number, but the use of alcohol in cars already running is difficult because they require major modifications to fuel systems. However, the use of conventional oxygenator like MTBE does not pose any such problems and this is the reason why in France the car engine manufacturers do not give a guarantee

for their engines if ethyl alcohol is used as the only oxygenator of gasoline.

It has been established that oxygenation through oxygenators do not bring about any change in NO_x in gasoline emissions, a pollutant which causes 50% of the traffic pollution.

Alcohol binds water and can lead to a phase separation in alcohol-containing gasoline, especially at low temperature. In order to minimize this risk, alcohol has to be added to the gasoline at the filling stations which implies transporting ethyl alcohol to numerous filling stations littered across the state and the country. Only a few sugar producing states produce alcohol in the country. There will be a major logistic problem involved in ferrying ethyl alcohol to the various filling stations.

By 2000 AD, the government proposes that only unleaded petrol to be used throughout the country and the motor vehicles be all equipped with catalytic converters, so that pollution menace from gasoline would be adequately checked and contained. The use of oxygenators in gasoline would then exclusively serve as octane booster.

ETBE from ethyl alcohol can also be used as an oxygenator but compared to MTBE it has a lower motor octane number. While MTBE has a motor octane number ranging between 115-123, ETBE's octane number ranges from 110-113. Moreover, conversion of ethyl alcohol into value added chemicals or its exports would be far more economically beneficial than converting it into ETBE. Internationally also, methanol being a cheaper raw material, MTBE is the preferred octane booster.

Realizing the increasing use of MTBE as an octane booster, the government has cleared the Indian Oil Corporation (IOC) proposal to put up an MTBE plant. IOC is procuring technology from CDT (Catalytic Distillation Technologies) of US for its 45,000 TP

A MTBE unit at its Gujarat refinery in Baroda. IOC is paying total technology fees of 902,500 US \$. The entire output from this new MTBE unit will be used by IOC to increase octane number of motor spirit.

In the Indian context no experimentation whatsoever has yet been conducted for funding out operational compatibility of motor engines to alcohol/neat alcohol as an oxygenator.

Investment in Refineries

The installed refinery capacity available in the country would go up to the level of 1190 lakh tons during 2000 AD (Annexured V) by which time the projected crude demand would be 1000 lakh tons but the crude availability within the country is not expected to go beyond 420 lakh tons. Currently also the refinery capacity is far in excess of the crude availability which is only 320 lakh quintals and thus works out to be a meagre 44% of the refinery capacity. For optimum utilization of the substantial refinery capacity in the country costing a whopping Rs. 11515 crores (Annexure VI) and keeping in mind that domestic crude production is woefully short of the total projected demand, it is imperative that crude needs to be imported and there is no sense in replacing crude imports with alcohol blending.

Energy analysis of Fuel Ethanol

A detailed analysis had been carried out in the United States on the energy balance in producing ethyl alcohol and utilizing it as gasohol/fuel. The amount of petroleum displaced by the use of alcohol from maize as a motor spirit was related to its calorific value (29 GJ/MT for ethanol against 43.5 GJ/MT for motor spirit). The results of the energy analysis are given in Table 3.

The outcome of this analysis clearly demonstrates that a saving of 35 GJ of petroleum energy is at the cost of expending 100% more primary input energy of 70.30 GJ.

Conclusion

In the light of the discussion presented in earlier sections, it can be concluded that the molasses rich state of Uttar Pradesh does not have the required level of alcohol availability to sustain even the state's demand of alcohol either for fuel blending or as an oxygenator. The technical evaluation, the energy analysis and availability of surplus refining capacity further suggest the futility in pursuing any fuel alcohol programme.

Table 3 — Energy analysis of ethyl alcohol production as fuel
GJ/MT ethanol

Agricultural input (3.35 MT maize)*	26.60
Process energy	
Fermentation	08.90
Distillation	19.80
Evaporation and drying	22.80
Credit for by-product	-6.80
Total input	70.30
Calorific value of ethanol	29.00
Motor spirit processing credit	06.00
Total output	35.00

*Molasses based alcohol has around the same energy input

The best viable alternative for the state in the event of having surplus alcohol, if any, is to maintain at least 20% of the state's total traditional requirement as a buffer stock and remaining surplus, if any, could be more pragmatically and economically exported outside the country rather than using it for fuel blend or oxygenator. The benefits from export of alcohol, vis-a-vis replacement of crude by alcohol has been brought out in the calculation back up provided in Annexure VII from which it can be seen that MT of ethyl alcohol fetches about 450-500 USD. The equivalent quantity of petrol and diesel (taken together for computation convenience) would require the import of 240 MT of crude which at the present level of Custom Duty (25%) would cost about 494 USD. There is thus a definite foreign exchange gain in importing crude rather than replacing it with alcohol which can be gainfully exported abroad. Besides, the import of 2.40 MT of crude would also result in the availability of fractions like kerosene, LPG, naphtha, fuel oil, AT fuel, paraffin wax etc. whose value addition at the current average international price of 180 USD/MT works out to about 300 USD which otherwise would have to be spent on the import of these fractions

Annexure I — Consumption of motor spirit (Petrol) and Diesel (HSDO)

States	1990-91				1991-92				1992-93				1993-94				1994-95				Unit:MT
	MS	HSDO	MS	HSDO	MS	HSDO	MS	HSDO	MS	HSDO	MS	HSDO	MS	HSDO	MS	HSDO	MS	HSDO	MS	HSDO	
Andhra Pradesh	217000	1719000	220000	1875000	225000	1875000	225000	1875000	242000	1875000	242000	1875000	242000	2191000	270000	2422000					
Gujarat	277000	1329000	283000	1458000	276000	1458000	276000	1458000	311000	1559000	311000	1559000	311000	1772000	327000	1920000					
Maharashtra	581000	2615000	576000	2691000	557000	2691000	557000	2691000	582000	2803000	582000	2803000	582000	2970000	629000	3227000					
Tamilnadu	238000	2006000	241000	2097000	244000	2097000	244000	2097000	262000	2144000	262000	2144000	262000	2233000	291000	2444000					
Uttar Pradesh	337000	2651000	345000	2979000	340000	2979000	340000	2979000	360000	3187000	360000	3187000	360000	3362000	367000	3615000					
Country total	3545000	21139000	3573000	22679000	3615000	22679000	3615000	22679000	3834000	24451000	3834000	24451000	3834000	25878000	4141000	28261000					
% of HSDO used in road and agri transport		81.10%		82.10%		82.10%		82.10%		82.80%		82.80%		82.70%		82.75%					

Consumption of MS (Petrol) and diesel (HSDO) in transport

States	1990-91				1991-92				1992-93				1993-94				1994-95				Unit:MT
	MS	HSDO	MS	HSDO	MS	HSDO	MS	HSDO	MS	HSDO	MS	HSDO	MS	HSDO	MS	HSDO	MS	HSDO	MS	HSDO	
Andhra Pradesh	217000	1394109	220000	1539375	225000	1539375	225000	1539375	242000	1552500	242000	1552500	242000	1811957	270000	2004205					
Gujarat	277000	1077819	283000	1197018	276000	1197018	276000	1197018	311000	1290852	311000	1290852	311000	1465444	327000	1588800					
Maharashtra	581000	2120765	576000	2209311	557000	2209311	557000	2209311	582000	2320884	582000	2320884	582000	2456190	629000	2670343					
Tamilnadu	238000	1626866	241000	1721637	244000	1721637	244000	1721637	262000	1775232	262000	1775232	262000	1846691	291000	2022410					
Uttar Pradesh	337000	2149961	345000	2445759	340000	2445759	340000	2445759	360000	2638836	360000	2638836	360000	2780374	367000	2991413					
Country total	3545000	17143729	3573000	18619459	3615000	18619459	3615000	18619459	3834000	20245428	3834000	20245428	3834000	21401106	4141000	23385978					

Source: Indian Petroleum and Natural Gas Statistics (1990-91 - 1994-95)

Annexure II--Requirement of ethanol for substitution of MS and diesel in transport

Assumptions:

Experimentation by IIP, Dehradun has been conducted with E10 & above and hence a min. 10% ethanol for petrol(MS) blending has been considered.
Experimentation by IIP, Dehradun has been with a min. 15% diesel replacement by methanol/ethanol and hence 15% of diesel requirement has been taken in terms of ethanol.

States	1990-91		1991-92		1992-93		1993-94		1994-95		Unit: MT
	Ethanol for MS	Ethanol for HSDO	Ethanol for MS	Ethanol for HSDO	Ethanol for MS	Ethanol for HSDO	Ethanol for MS	Ethanol for HSDO	Ethanol for MS	Ethanol for HSDO	
Andhra Pradesh	21700	209116	22000	230906	22500	232875	24200	271794	27000	300631	
Gujarat	27700	161673	28300	179553	27600	193628	31100	219817	32700	238320	
Maharashtra	58100	318115	57600	331397	55700	348133	58200	368429	62900	400551	
Tamilnadu	23800	244030	24100	258246	24400	266285	26200	277004	29100	303362	
Uttar Pradesh	33700	322494	34500	366864	34000	395825	36000	417056	36700	448712	
Country total	354500	2571559	357300	2792919	361500	3036814	383400	3210166	414100	3507897	

Annexure III — Requirement of ethanol for substitution of MS and DHSD in transport

Uttar Pradesh -- Actuals and projections

Year	Ethanol reqmnt. for MS (MT)	Ethanol reqmt. for diesel (MT)	Total ethanol reqmnt. for MS and diesel (MT)	Total ethanol reqmnt for MS & diesel (lakh ltr)	Production	Alcohol scenario in the State Consumption						
						Total production (lakh Ltr)	Industry & others (lakh ltr)	Potable liquor (lakh ltr)	Export to states (lakh ltr)	Export abroad (lakh ltr)	Offtake by new units (lakh Ltr)	Total consump. (lakh Ltr)
1990-91	33700	322294	356194	3789.30	3436.30	1319.76	765.75	956.56	289.17	-	-	3331.24
1991-92	34500	366864	401364	4269.83	3592.60	1438.47	773.04	937.63	258.74	-	-	3407.88
1992-93	34000	395825	429825	4572.61	2929.30	1171.09	839.09	781.05	141.85	-	-	2933.08
1993-94	36000	417056	453056	4819.75	2914.30	1014.62	861.84	530.92	0.00	-	-	2407.35
1994-95	36700	448712	485412	5163.96	2976.68	1630.24	1001.98	234.04	0.00	-	-	2866.26
Projections:												
1995-96	37489	487301	524790	5582.87	4398.75	1750.38	1152.28	257.44	-	-	-	3160.10
1996-97	38426	529209	567635	6038.67	4151.05	1951.73	1325.12	283.19	-	-	-	3560.04
1997-98	39387	574721	614108	6533.06	4363.95	2176.79	1523.89	311.51	-	652.40	-	4664.58
1998-99	40372	624147	664519	7069.35	4588.19	2428.41	1752.47	342.66	-	978.59	-	5502.13
1999-2000	41381	677824	719205	7651.11	4745.57	2709.74	2015.34	376.92	-	1630.99	-	6732.99

Assumptions:

1. A 10% ethanol blend is considered for MS(petrol).
2. 15% diesel replacement by ethanol is considered.
3. Compounded growth rate of 2.15% has been considered in MS(petrol) consumption.
4. Compounded growth rate of 8.60% has been considered in diesel consumption.
5. Alcohol production has been projected on the basis of 85% utilization of total molasses production.
6. Total alcohol assurances as existing on date is 1630.99 lakh Ltrs. It has been assumed that 40% of these assurances will mature by 1997-98 followed by 60% in 1998-99 and the remaining by 2000 AD.
7. Alcohol consumption for chemical and potable sector has been projected on basis of historical trend analysis.
8. Alcohol requirement for export to other states projected on the basis of 10% growth over the 1994-95 figure which happened to be the lowest in the past many years.

Annexure IV — Active alcohol assurances as on 14.09.96
(given by the state of Uttar Pradesh)

Units	Chemical/s	Location	Alcohol assurance (lakh ltrs)
Accurate Chemical	Ethyl acetate	Sahibabad	25.11
Coats of India	Printing ink	Noida	2.88
Dhampur Sugarmills	Ethyl acetate	Bijnore	21.60
Easter India Ltd	Ethyl acetate	Ghaziabad	23.04
Easter India Ltd	Acetic acid	Barabanki	235.00
Ghaziabad Organic	Acetic acid	Ghaziabad	65.10
Integrated Organics	Di-Ethyl phthalate	Sikandrabad	32.00
Karkar Organics	Ethyl acetate	Sahibabad	20.85
Oswal agro	LDPE	Shahjahanpur	450.00
Shivalik Microfood	Ethyl acetate		
Somaiya Organics	Acetic acid	Barabanki	135.41
Vam Organics	Acetaldehyde	Gajraula	620.00
Total assurances:			1630.99

Note: The above assurances do not include the molasses assurances to the extent of 1332 lakh qtls which in alcohol terms is equal to 30 lakh litres

Annexure V — Installed finery capacity available in India
As on 1 Apr.95

Company	Location	Capacity (Lakh Tons)
IOC	Digboi*	6.50
BPCL	Bombay	60.00
HPCL	Bombay	55.00
HPCL	V. Patnam	45.00
IOC	Guwahati	10.00
IOC	Barauni*	38.00
IOC	Koyali*	125.00
IOC	Haldia	27.50
IOC	Mathura	75.00
CRL	Cochin*	75.00
MRL	Madras	65.00
BRPL	Assam*	23.50
MRL	Narimanam	5.00
IOC	Panipat@	60.00
HPCL	Mangalore@	30.00
IOC	Numaligarh@	30.00
Total Refining Capacity		730.50
*Considering expansions being undertaken		
@Under Implementation during 8th plan		
Projected Refining Capacity:		(lakh tons)
By 2002		1110
By 2007		1190 [#]
[#] Estimates based on refinery plans currently being pursued.		
Source: Indian Petroleum and Natural Gas Statistics 1993-94 and Industrial Development Services		

(Contd)

Annexure V (Contd)

Year	Crude production (lakh tons)	Crude import (lakh tons)*	Total crude available	Projected demand (lakh tons)
1990-91	330.20	207.00	537.20	
1991-92	303.50	240.00	543.50	
1992-93	269.50	292.50	562.00	
1993-94	270.30	308.20	578.50	
1994-95	320.00	273.50	593.50	
Projections:				
1995-96	320	260.00	580	600
1996-97	342	330.00	672	681
1997-98	366	363.00	729	773
1998-99	392	435.60	828	877
1999-2000	420	544.50	965	1000
Conclusion:				
Adequate refinery capacity is available in the country to cater to the crude demand by 2000 AD. Presently refining capacity is in excess of the crude demand by about 20%				

Annexure VI — Capital investment and employed in petroleum Sector
As on: 1 April 94

Total capital investment in the petroleum sector: 24925.81 Rs crores

Paid up capital 1931.74 Rs crores

Total Loans 22994.07 Rs crores

Total capital employed in the petroleum sector: 29803.10 Rs crores

Net fixed assets 18800.56 Rs crores

Working capital* 11002.44 Rs crores

Total capital investment in refineries: 9713.12 Rs crores

Paid up capital 468.75 Rs crores

Total Loans 9244.37 Rs crores

Total capital employed in refineries: 11515.03 Rs crores

Net fixed assets 5794.17 Rs crores

Working capital* 5720.86 Rs crores

* excludes capital work in progress and capital goods

Source: Indian Petroleum and Natural Gas Statistics 1993-94

Annexure VII — Calculation backup	
Crude (World Avg. gravity of 34 Deg API)	7.33 Barrels = 1 MT,
Barrel price:	22.50 USD per barrel
1 MT crude (basic) =	164.93 USD
Custom Duty @ 25%	41.23 USD
Total cost:	206.16 USD
1 MT Ethanol current export price is:	450-500 USD
22652000 MT HSD and petrol obtained from	54296000 MT Crude
1 MT HSD and petrol obtained from	2.40 MT Crude
Import value of 2.40 MT Crude	494.15 USD
Fractions from 2.40 MT Crude: (other than HSD and petrol)	
LPG	0.058 MT LSHS/RFO 0.183 MT
Naphtha	0.206 MT Fuel Oils 0.455 MT
Kerosene	0.232 MT Lube Oils 0.022 MT
AT Fuel	0.079 MT Bitumen 0.083 MT
LD Oil	0.065 MT Petroleum coke 0.010 MT
Furnace Oil	0.272 MT Paraffin wax 0.004 MT
	Total 1.669 MT
Avg. international price of the above petroleum products =	180 USD/MT Value of the above fraction = 300.40 USD

Evaluation of *Hibiscus sabdariffa* and *Gmelina arborea* as Raw Materials for Production of High α -cellulose Pulp

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High α -cellulose was extracted from two fast growing plants viz. *Hibiscus sabdariffa* (an annual plant) and *Gmelina arborea* (a perennial plant), by following water pre- hydrolysis sulphate process. Proximate chemical analysis showed high pentosan contents in wood raw materials (18.4% in *H. sabdariffa* and 20.52% in *G. arborea*), while lignin contents are comparatively low in *H. sabdariffa* (17.90%). Pre-hydrolysis was carried out at three different temperatures viz. 140, 150 and 160°C for 2.5 and 3 h for *H. sabdariffa*, while for *G. arborea*, pre-hydrolysis was carried out at 150, 160 and 165°C for the same periods of time. Kraft cooking was done for all the batches of pre-hydrolyzed chips and the characteristics of unbleached pulps obtained were evaluated. The yields of unbleached pulp were within the range 29- 40.3 %, while ratio of pentosan removal was 83.65-93.4 %. Selected batches of unbleached pulp were bleached using C-E- H-E-H-dil HCl sequence under controlled conditions. Bleached pulps with brightness 86- 88% were obtained, having α -cellulose 93.2-95.6 % with degree of polymerization varying from 940-996. The α -celluloses were further characterized with the help of IR, X-ray, SEM and thermal analyses.

1 Introduction

Many forest based cellulosic raw materials have been identified and commercially utilized for preparation of high α - cellulose pulps, since the first man made fibre industry came into existence around the turn of nineteenth century.

The high α -cellulose or dissolving cellulose finds applications in many chemical and paper making end uses and is principally used for manufacture of esters and ethers, lacquers, plastics, vulcanized fibre, artificial leathers, sponges, and grafted products etc.¹ Studies on preparation of high α -cellulose pulp from hard and soft woods, bamboo and reed, cotton litters, bagasse and such other agricultural residues have been made by many workers in India and abroad²⁻¹². During last three decades, many fast growing annual and perennial plant species have been identified as alternative source of raw material for pulp and paper making.¹³⁻¹⁸ But very little information is available on the use of fast growing plant materials, both

annual and perennial, for production of high α -cellulose pulps.¹⁹⁻²¹ Highly purified cellulose or dissolving cellulose has to conform to certain rigid specifications.²²⁻²⁴ There is wide variation in the compositional characteristics of each and every cellulose bearing plant and as such, it is necessary to examine every variety individually for its usability for preparation of highly purified cellulose.

The present work was, undertaken to isolate α -cellulose from *Hibiscus sabdariffa* Linn (Roselle, Lal ambari in Hindi), an annual plant and *Gmelina arborea* Roxb (Gumhar in Hindi), a perennial plant and characteristic properties of the α -celluloses so obtained were evaluated.

H. sabdariffa, HS-7910 can be grown in the temperate or tropical climates and it has long been cultivated in many parts of the world including India. It can be cultivated in prepared sites like jute and kenaff. Though ready statistics on the present level of production in the country are not available, a substantial quantity of this plant is grown for use as fuel wood and fodder. The bast portion of the plant

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is used for making ropes and twines. The stem including bark yields high quality cellulose. So also, *Gmelina arborea*, a perennial tree of moderate size (height 3.05 - 4 m) already identified as a fast growing plant for Asiatic region²⁵, can also be grown in prepared sites. It is also abundantly available in the forests. The present level of production can be increased by adopting appropriate agro- technology²⁶, as both the plants were found to attain luxuriant growth in the agroclimatic conditions of north eastern region of India.

2 Materials and methods

The biomass material used for the present study was obtained from the plants cultivated in the experimental farm of Regional Research Laboratory, Jorhat, India.

A 5 year old *G. arborea* plant was selected for the experimental work, as it was found to be the optimum age of the plant for economic yield of cellulose. This was determined not only from CAI (current annual increment) and MAI (mean annual increment) values, but also physically found out while ascertaining the biomass yields of the plant of different ages of maturity^{26,27}. Therefore, the stem portion of the plant was debarked and then chips of 2.5 cm length and 1.5-2 cm width were prepared. In case of *H. sabdariffa*, fully matured plants (6-7 months old) without debarking were cut into pieces of 2.5 cm length.

The chips as prepared above, were dried to moisture level 12-15% and then used for the experimental work on oven dry (o.d.) basis.

2.1 Proximate chemical analyses

Air dried chips were made into powder and screened through a 40 mesh wire. Powder (-40 and +60 mesh) is taken for chemical analysis and Tappi standard methods²⁸ were followed. The results obtained are given in Table 1.

2.2 pre-hydrolysis and Pulping of wood chips

Water pre-hydrolysis and kraft pulping processes were adopted. Both pre-hydrolysis and pulping were carried out in a ten litre capacity electrically heated, rotary, stainless steel digester. The chips were pre-hydrolyzed at material to liquor ratio 1:5. Nearly 1 kg of wood chips (as oven dry matter) was charged in the autoclave and subsequently required amount of deionized water was added. The hydrolysis was

Table 1 — Proximate chemical analysis of *Hibiscus sabdariffa* and *Gmelina arborea*

	<i>H.sabdariffa</i>	<i>G. arborea</i>
Solubility in :		
Cold water, %	4.04	3.85
Hot water, %	7.30	6.45
1% Alkali, %	24.42	18.90
Alcohol benzene (1:2), %	4.81	3.75
Lignin %	17.90	25.50
Pentosan %	18.40	20.52
Cross & Bevan cellulose %	58.45	57.30
Ash %	1.12	0.92

carried out at different conditions (Table 2). The pre-hydrolyzed chips were washed first with deionized water and then with distilled water and finally air dried. The pre-hydrolyzed chips of *H. sabdariffa*, obtained after 2.5 and 3 h cooking at different temperatures, were digested with 16% active alkali ($\text{NaOH} + \text{Na}_2\text{S}$) as Na_2O for 3 h at $160 \pm 2^\circ\text{C}$ maintaining sulphidity at 20%. So also, cooking of pre-hydrolyzed chips of *Gmelina arborea* was carried out with 18% active alkali as Na_2O at sulphidity 25% for 3 h at $163 \pm 2^\circ\text{C}$. In both the cases, the time taken to reach the maximum temperature varied between 45 and 60 min. Nearly 0.5 kg of oven dry pre-hydrolyzed chips was taken for each digestion. At the end of the digestion period, the pulp was discharged from the autoclave on a 60 mesh sieve and washed thoroughly, first with deionized water and then distilled water and finally air dried and analyzed. Pulping conditions and analytical data on unbleached pulp are given in Table 3. Morphological characteristics of the unbleached fibres, taken from batch 2 and 11, were determined by using a Dokuval photomicroscope (JEOL, Japan) at different magnifications. About 200 fibres of various sizes were measured for their length, diameter, cellwall thickness and the average values of the results are given in Table 4.

Table 2 — Prehydrolysis conditions and analytical data of prehydrolyzed chips

Sample Cooking time, h	<i>H. sabdariffa</i>						<i>G. arborea</i>					
	2.5			3			2.5			3		
Cooking temp., °C	140	150	160	140	150	160	150	160	165	150	160	165
Batch No.	1	2	3	4	5	6	7	8	9	10	11	12
pH of prehy. liquor	5.9	6.4	6.8	6.3	6.8	7.2	4.1	3.8	3.6	3.9	3.5	3.1
Yield, %	82.5	80.0	78.1	80.2	77.5	74.0	87.0	83.5	79.9	83.0	81.5	77.5
Pentosan, %	12.2	10.1	9.2	11.0	9.3	8.1	11.5	9.8	8.7	10.0	8.1	6.3
Ratio of pentosan removal, * %	45.3	56.1	61.0	52.1	60.8	67.6	30.03	42.78	51.39	41.96	53.84	65.86
Ratio of removed pentosan to dissolved matters**, %	47.6	51.6	51.2	48.4	49.7	47.3	33.04	37.07	36.56	35.29	41.61	41.86
Lignin, %	16.7	16.2	15.8	16.3	15.8	15.3	25.0	24.7	24.3	24.9	24.3	23.8
Ratio of lignin removal*, %	23.0	27.6	31.1	27.0	31.6	37.0	14.71	19.21	23.86	18.95	22.34	24.67
Ratio of removed lignin to dissolved matters**, %	23.6	24.7	25.4	24.4	25.1	25.2	28.85	29.55	30.27	28.43	30.79	31.36
Alcohol benzene solubility, %	5.9	6.4	6.8	6.3	6.8	7.2	4.4	5.6	6.3	5.7	6.6	7.2

$$\text{*Ratio of pentosan/lignin removal} = \frac{A - B \times \text{yield}}{A} \times 100$$

$$\text{**Ratio of removed pentosan/lignin to dissolved matters} = \frac{A - B \times \text{yield}}{100 - \text{yield}} \times 100$$

where A : Pentosan/lignin in original wood ; B : pentosan/lignin in the prehydrolysed wood⁴

2.3 Bleaching

The screened unbleached pulp from each cook was bleached by a typical multistage bleaching sequence involving chlorination (C), alkali extraction (E), hypochlorite treatment (H), alkali extraction (E) and hypochlorite treatment (H) with intermediate washings with deionized water after each stage. The conditions of bleaching maintained in each stage are given in Table 5. Finally, a mild HCl acid treatment was given to the bleached pulp in order to improve brightness and to prevent colour reversion.⁶

2.4 Evaluation and Characterization of bleached pulps

The bleached pulp yields were determined. Pentosan, lignin, α -, β - and γ -celluloses, copper number, ash and brightness were determined as per Tappi standard methods.²⁸ Degree of polymerization (DP)

and carboxyl contents were determined as per methods suggested elsewhere.^{4,29} The results are given in Table 6.

Infrared (IR) spectra of α -cellulose was recorded on a Perkin Elmer spectrometer (Model 2000 FTIR) using the KBr disk technique from 4000 to 450 cm^{-1} with a resolution of 2 cm^{-1} with five scans per sample. X-ray diffraction pattern were recorded using a computer controlled X-ray diffractometer (Type JDX-11 P3A, JEOL, Japan) with pulse height analyser and scintillation counter with scintillator NaI (T1) single crystal.

2.5 Scanning electron microscopy

Fibres in the pulp samples were separated and mounted on specimen holders with the help of electroconductive tapes. The samples were coated with gold in an ion-sputter coater (JFC 100, JEOL, Japan)

Table 3 — Conditions of sulphate pulping and analysis of unbleached pulp

Sample	<i>H. sabdariffa</i>						<i>G. arborea</i>					
	2.5			3			2.5			3		
Prehydrolysis time, h	140	150	160	140	150	160	150	160	165	150	160	165
Prehydrolysis cooking temp., °C												
Batch No.	1	2	3	4	5	6	7	8	9	10	11	12
Yield, %	34.6	33.0	31.8	33.7	31.3	29.0	40.3	37.5	36.0	37.7	36.5	34.0
Pentosan, %	5.1	4.7	4.4	4.8	4.5	4.2	5.8	5.1	4.8	5.2	4.9	4.3
Ratio of pentosan removal, %	90.4	91.6	92.4	91.2	92.4	93.4	83.65	86.63	87.92	86.29	87.49	89.78
Ratio of removed, pentosan to dissolved matter, %	25.4	25.2	24.9	25.3	24.7	24.2	20.24	19.82	19.64	19.81	19.70	19.45
Lignin, %	3.3	3.0	2.8	3.1	2.8	2.4	3.9	3.4	3.1	3.6	3.2	2.8
Ratio of lignin removal, %	93.6	94.5	95.0	94.2	95.1	96.1	93.84	95.00	95.62	94.68	95.42	96.27
Ratio of removed lignin to dissolved matters, %	25.6	25.2	24.9	25.4	24.8	24.2	40.08	38.76	38.10	38.75	38.31	37.19
Permanganate number	7.3	6.4	5.6	6.5	5.4	5.1	11.2	8.7	7.5	9.0	8.2	6.0
Ash, %	0.20	0.18	0.17	0.18	0.17	0.16	0.23	0.21	0.19	0.19	0.18	0.17

*Based on original wood on oven dry basis.

Table 4 — Morphological characteristics of pulp fibres

	<i>H. sabdariffa</i>			<i>G. arborea</i>		
	Maximum	Minimum	Average	Maximum	Minimum	Average
Fibre length, L (mm)	2.5	0.5	1.74	1.20	0.45	0.95
Fibre diameter, D, (μ m)	24.5	12.0	21.00	25	10	22
Lumen diameter, d, (μ m)	16.0	7.2	13.90	18.2	9.4	16.5
Cell wall thickness, W, (μ m)	4.8	3.5	4.26	3.8	2.0	2.3
Slenderness ratio, (L/D)	—	—	82.86	—	—	43.18
Runkel ratio, (2 W/d)	—	—	0.61	—	—	0.28
Flexibility coefficient, (d/D x 100)	—	—	66.19	—	—	75.0
Wall fraction, (2 W/Dx100)	—	—	40.57	—	—	20.91
Ratio of cell wall thickness to fibre diameter, (2 W/D)	—	—	0.41	—	—	0.21
Ratio of cell wall thickness to lumen diameter (W/d)	—	—	0.31	—	—	0.14
Shape factor (D^2-d^2/D^2+d^2)	—	—	0.39	—	—	0.28

Table 5 — Conditions of bleaching

Stages	Chemicals as available Cl ₂ or, % alkali on o.d. pulp	Consistency %	Temperature °C	Retention time min
Chlorination (C)	1.40-3	3	25	30
Alkali Extraction (E)	2	10	60	60
Hypochlorite (H)	0.75-1.25	10	45	90
Alkali Extraction (E)	1.5	10	60	60
Hypochlorite (H)	0.75-1.15	10	45	60
Dil HCl treatment	0.05 (V/V)	4	25	30

Table 6 — Analytical data on bleached pulps

Sample	<i>H. sabdariffa</i>					<i>G. arborea</i>		
Prehydrolysis cooking time, h	2.5		3		2.5		3	
Prehydrolysis Cooking temp. °C	150	150	160	160	165	150	160	165
Batch No.	2	5	6	8	9	10	11	12
Yield, * %	27.9	27.5	27.0	29.6	29.2	28.9	28.5	28.1
α-cellulose, %	93.2	94.1	93.2	93.5	94.7	94.1	95.1	95.6
β-cellulose, %	2.60	2.42	2.33	3.08	2.84	2.97	2.88	2.75
γ-cellulose, %	0.57	0.50	0.48	0.67	0.58	0.68	0.60	0.51
Pentosan, %	2.60	2.45	2.35	2.46	2.37	2.37	2.20	2.11
Copper Number	0.076	0.061	0.053	0.11	0.067	0.08	0.071	0.062
Ash, %	0.07	0.05	0.05	0.08	0.07	0.07	0.06	0.06
D.P., average	940	900	880	996	987	984	970	958
Carboxyl content, m eq/100g	3.1	3.3	—	—	3.1	—	3.25	3.0
Brightness, %	87	88	87	86	87	86	87	88

*Results on original wood on oven dry basis.

in low vacuum with a layer 150-200 nm thick, and observed in a JEOL, JSM-35M-35 CF electron microscope at 15 kV an accelerating potential.

2.6 Thermal Behaviour

Thermogravimetry (TG) and differential thermogravimetry (DTG) were carried out using a Shimadzu Thermal Analyser 30. The mass of the samples of cellulose were in the range 7.17-9.43 mg. α-alumina was used as reference material and the

temperature ranged from 30 to 800°C at heating rate 10°C min⁻¹, in static air atmosphere.

3 Results and Discussion

Analytical data for *H. sabdariffa* and *G. arborea* presented in Table 1 indicate that the raw materials might be suitable for preparing high α-cellulose pulp. The pentosan contents in both the plant materials are very high whereas lignin is relatively low in *H. sabdariffa* in comparison to *G. arborea*; the ash content is higher in *H. sabdariffa* (1.12%) than that

Table 7.a — Thermal analysis data for celluloses at heating rate $10^{\circ}\text{C min}^{-1}$

	DTG peak temperature ($^{\circ}\text{C}$)			% weight loss
	I	II	III	
Cellulose A	85	290	470	61.2
Cellulose B	80	300	—	57.5
Cellulose C	100	300	—	57.5

Key : I, II, III — pre, second and third stages.

Table 7.b — Dynamic thermogravimetry data for celluloses at heating rate $10^{\circ}\text{C min}^{-1}$

	Temperature of active decomposition ($^{\circ}\text{C}$)		
Cellulose A	280	315	505
Cellulose B	300	325	540
Cellulose C	295	320	580

of in *G. arborea* (0.92%). The pre-hydrolysis was carried out at three different temperatures viz. 140, 150 and 160°C for 2.5 and 3 h, for *H. sabdariffa*, while for *G. arborea*, pre-hydrolysis was carried out at 150, 160 and 165°C for same periods of time. Table 2 gives the yields of pre-hydrolyzed chips, pH of pre-hydrolyzed liquors, ratio of pentosan and lignin removals etc. It is evident from the data obtained that percentage removal of constituents like lignin, pentosan and ash from original wood, increases with increase in temperature of pre-hydrolysis, while increase of pre-hydrolysis time at certain temperature does not effectively increase the removal of these constituents. The ratio of pentosan removal percentages increase with increase in temperature and duration of pre-hydrolysis. It would be seen that the rate of hydrolysis is governed by temperature and time⁴. It has been observed that the fibres from *H. sabdariffa* if pre-hydrolysis is carried out at a higher temperature and for longer period of time (160°C for 3-4 h). At lower temperatures and shorter periods of hydrolysis, the removal of pentosan is less. Pentosan and lignin are removed to the maximum with satisfactory yields from *H. sabdariffa* and *G. arborea*, when pre-hydrolysis is done at temperature range $140 - 150^{\circ}\text{C}$ and $150 - 165^{\circ}\text{C}$ respectively for 2.5-3 h.

The sulphate cookings of the pre-hydrolyzed chips were carried out under conditions as mentioned earlier. Pentosan, lignin and KMnO_4 number of pulp decrease with the increase of time and temperature of cooking. Figs. 1(a,b) and (c,d) show the effect of pre-hydrolysis temperatures on yield, pentosan and lignin removal of unbleached pulps at 2.5 and 3h pre-hydrolysis of *H. sabdariffa* and *G. arborea* respectively.

The bleached pulps obtained from the selected batches and their characteristics are recorded in Table 6. High α -cellulose pulp with average yields ranging from 27.0-29.6% on o.d. basis of original raw material was obtained. α -cellulose of 92.9-95.6% could be obtained with acceptable brightness, D.P., pentosan and ash contents. These results are comparable to those of standard viscose grade dissolving cellulose²⁴.

Further, the α -cellulose obtained from *H. sabdariffa* (batch 5) and *G. arborea* (batch 12), (hereafter termed cellulose A and B respectively), were analysed with the help of IR, X-ray, thermogravimetry and scanning electron microscopy (SEM) techniques and compared with data obtained from similar analysis on a commercial rayon grade pulp (M/s Harihar Polyfibers, India) containing 95.5% α -cellulose and 0.05% ash (cellulose C).

The comparative IR spectra of celluloses A, B and C exhibit characteristic absorption bands of O-H stretching (3360 cm^{-1}), C-H stretching (2920 cm^{-1}), C-H bending (1380 cm^{-1}), -OH bending ($1320-1360\text{ cm}^{-1}$), etc.³⁰⁻³². The X-ray diffraction patterns of celluloses A, B and C indicate that the pulps were typical native cellulose, consisting of both crystalline and amorphous phases³³ (Fig.2).

The thermal curves (TG and DTG) for celluloses A, B and C are shown in Fig. 3, at heating rate $10^{\circ}\text{C min}^{-1}$. The thermal analysis data are given in Table 7(a). The dynamic TG and DTG curves show a major mass loss with maxima around 290 and 300°C for all the three celluloses. Table 7(b) gives initial, maximum and final temperatures of active decomposition represented at T_1 , T_2 and T_3 respectively. The percentage mass losses (57.5-61.3) in the active decomposition range for all the three celluloses are more or less comparable, though cellulose B shows minimum mass loss at higher initial temperature of active decomposition (300°C). It may be inferred that three

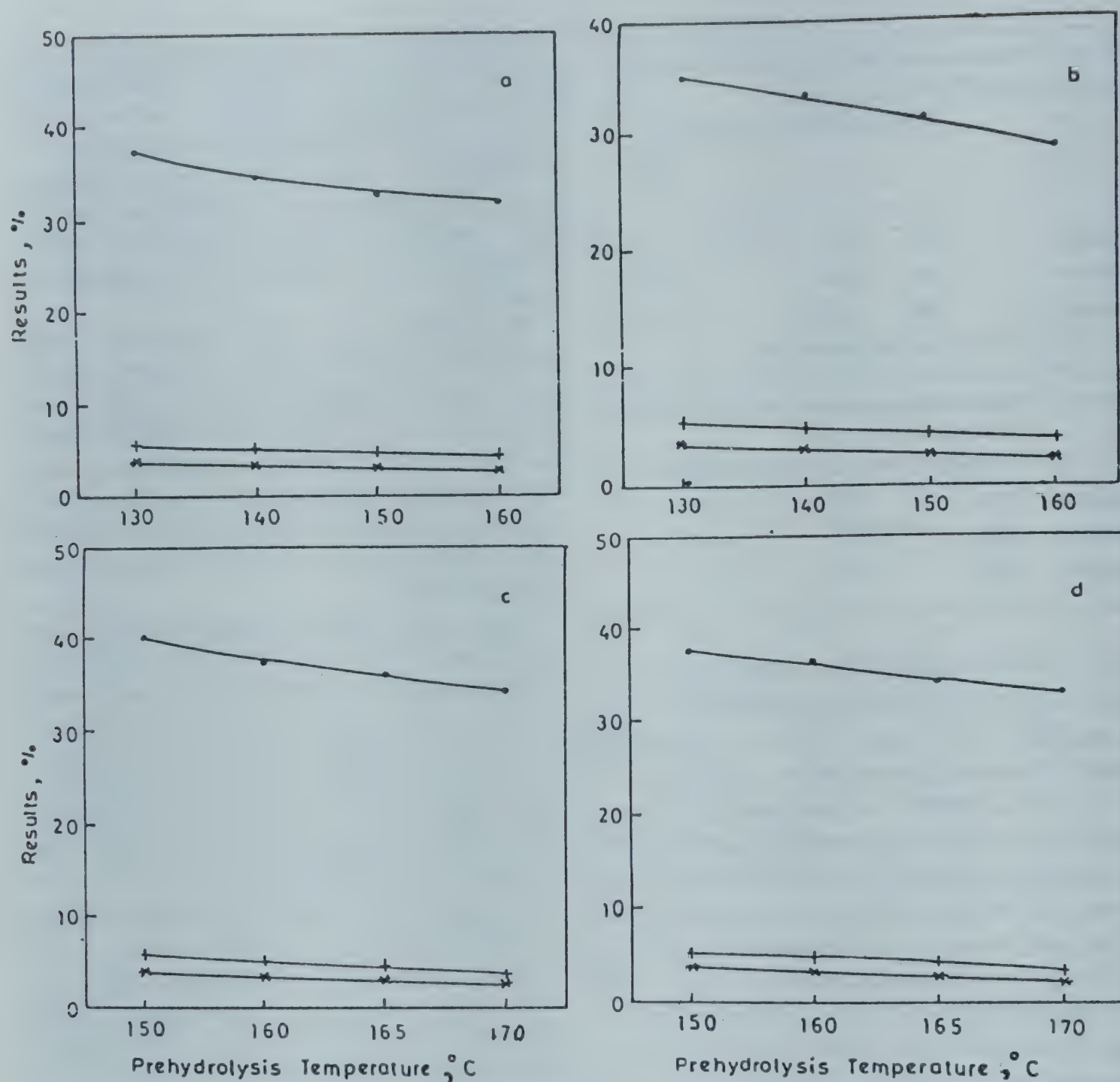


Fig. 1 — Effect of prehydrolysis temperature on yield (○—○—○—○), pentosan (+—+—+—+) and lignin (*—*—*—*) removal of unbleached pulp of *H. sabdariffa* (prehy. time a. 2.5 h and b. 3 h) and *G. arborea* (prehy. time c. 2.5 h and d. 3h).

main degradation steps namely initiation, propagation and carbonization, as suggested by Chatterjee and Conrad³⁴ are predominant for all the three celluloses.

Figs. 4(a) and (b) show the scanning electron micrographs of high α -cellulose pulp fibres from cellulose A and cellulose B. The micrographs show hollow and cylindrical fibres with distinct nodes. Fibrils are regularly arranged in a horizontal plane direction thereby indicating good quality fibres of flexible nature.

4 Conclusion

The α -cellulose extracted from *Hibiscus sabdariffa* and *Gmelina arborea* exhibits physico-chemical properties identical to those of α -cellulose available commercially. Adopting water pre-hydrolysis at 150°C for 3 h and sulphate pulping conditions of $160 \pm 2^\circ\text{C}$ for 3 h, good quality α -cellulose pulps could be produced from *H. sabdariffa*, so also pre-hydrolysis conditions of 150-165°C for 3 h, and sulphate cooking at $163 \pm 2^\circ\text{C}$ for 3 h at 25% sulphidity, are favourable to produce high α -cellulose pulp

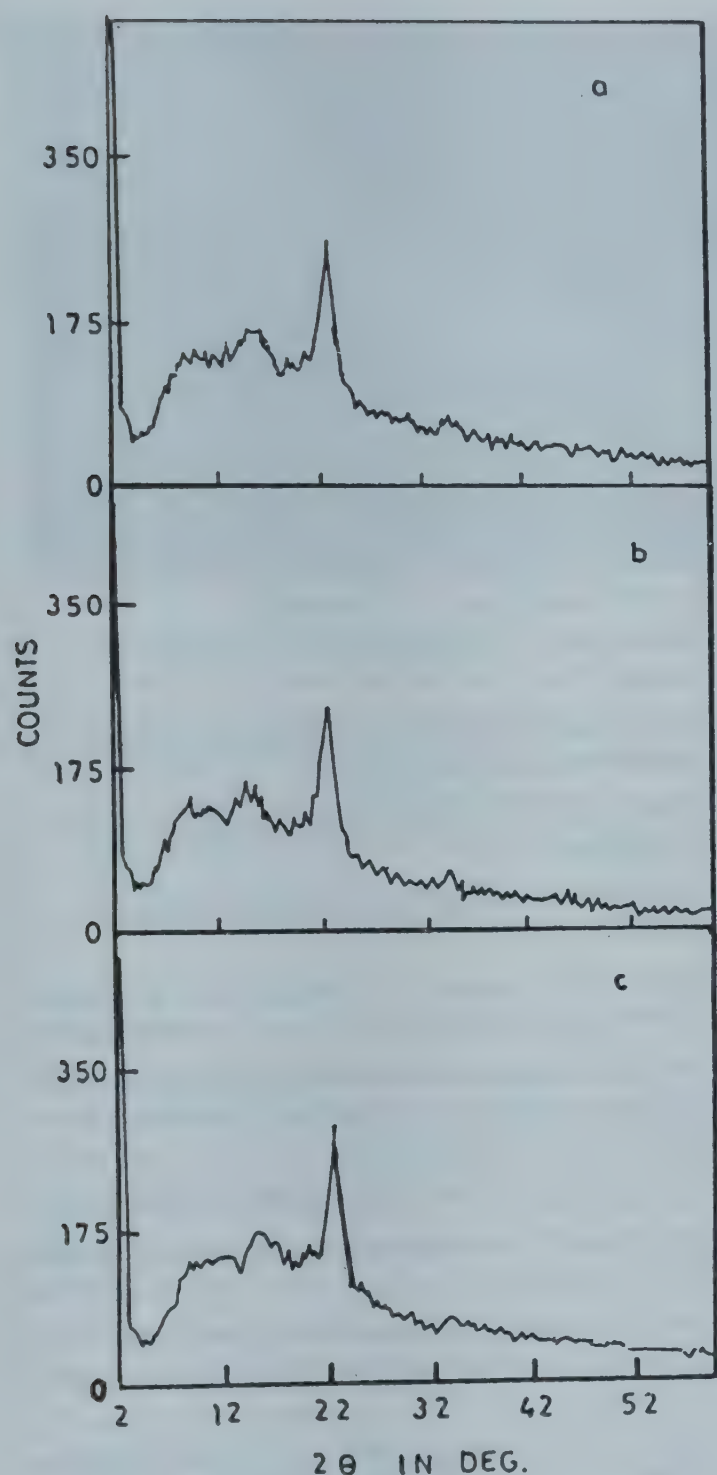


Fig. 2 — X-ray diffraction patterns of high α - cellulose pulp of a. *H. sabdariffa*, b. *G. arborea* and c. commercial rayon grade pulp:

from *G. arborea*. The results obtained in this investigation may form a basis for taking up commercial venture for production of high α -cellulose pulp from these plant raw materials. The cost of cultivation of these plants had been estimated at Rs 2500-3000 per hectare annually, while the return per hectare may yield approximately at Rs 20,000- 25,000. From these results it may be concluded that *H. sabdariffa* and *G. arborea* could be ideal plant sources for or isolation of pure cellulose.

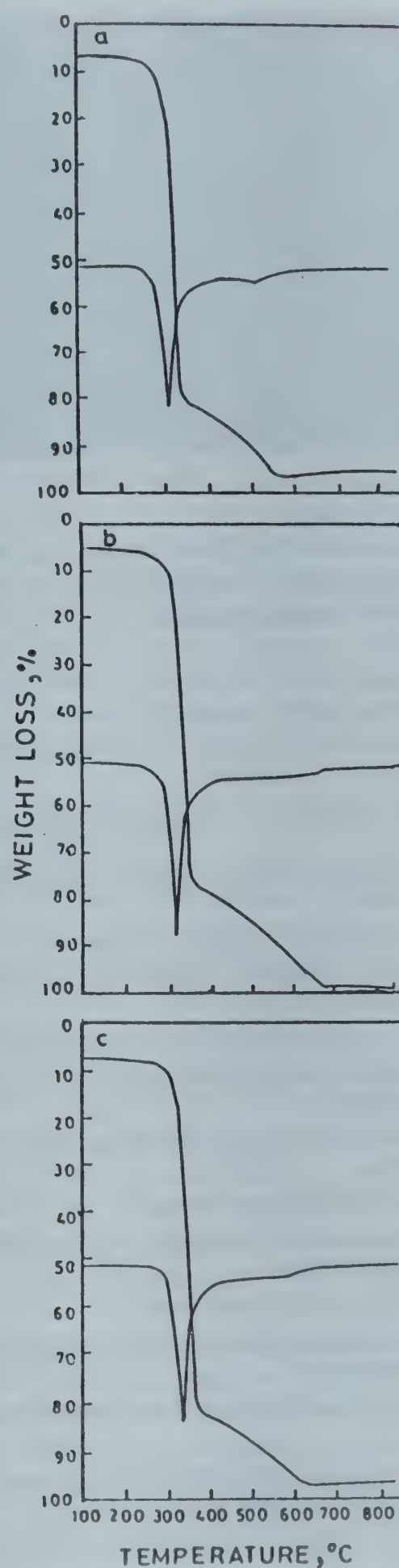


Fig. 3 — TG and DTG curves of high α - cellulose pulp of a. *H. sabdariffa*, b. *G. arborea* and c. commercial rayon grade pulp.

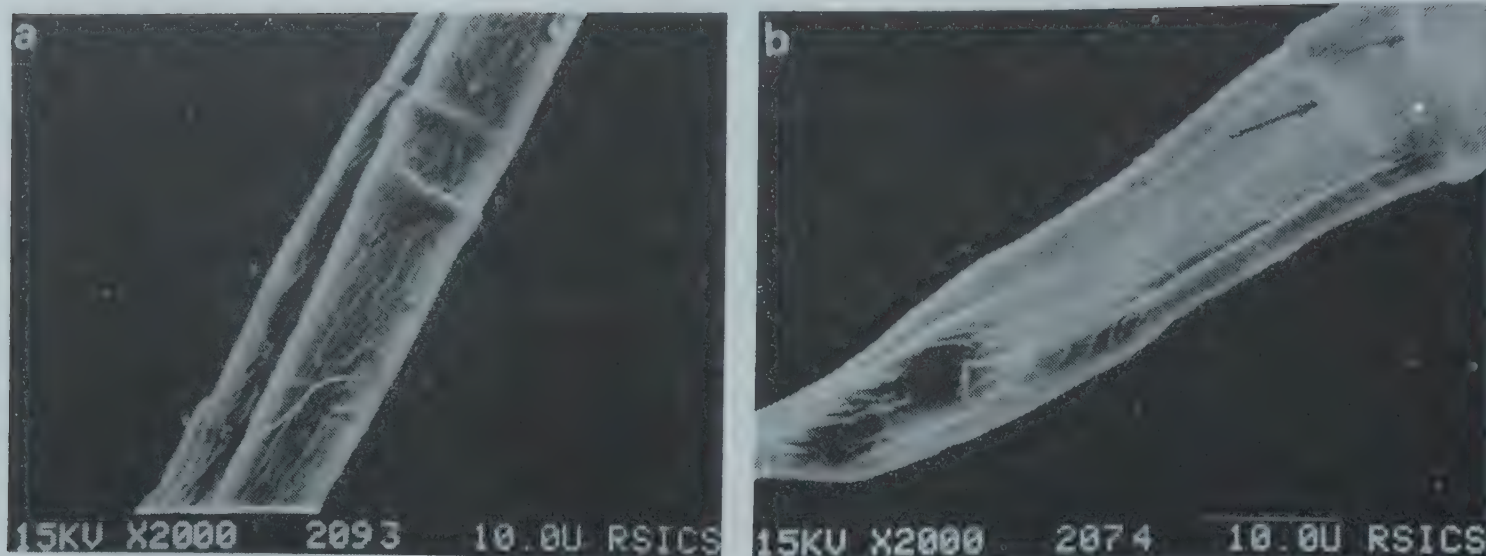


Fig. 4 — SEM of high α -cellulose pulp of a. *G. arborea* and b. *H. sabdariffa*.

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Effect of Fruit Maturity on Yield, Composition and Quality of Juice and Wine from Grapes

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The study examines the effect of fruit maturity on the yield, composition and quality of juice and wine from three local (*Chholtu red*, *Chholtu white*, and *Rangspay*) and two exotic cultivars (*Thompson seedless* and *Anab-e-Shahi*). As expected, berry weight, bunch weight, juice yield, TSS, pH, sugars, brix/acid ratio increased, whereas tannins and total titratable acidity decreased during maturation. The juice of exotic cultivars from second harvest (soluble solids: acid ratio of 27- 36, pH 3. 28-3. 52) was acceptable while the one from local cultivars rated unacceptable for drinking as a pure juice due to high astringency. However, good quality wine could be obtained from third harvest grapes in all the cultivars. *Thompson seedless* cultivar recorded highest fermentation rate and alcohol content. Local cultivars were not found to be suitable for the production of pure juice at any stage of harvest but could be successfully utilized for wine making because of high sugars, good colour, and flavour at the third maturity stage.

Introduction

Maturity of grapes is an important factor which determines the quality of juice and wine. Less mature grapes may yield watery juice and wine with high acid and little flavour while the over ripe berries result in poor quality juice and wine. Morris *et al.*¹ and Sims and Morris² have reported that more mature concord grapes produced superior juice compared to less matured grapes. Ough and Alley³ have found an optimum brix to acid ratio of 30-32 for production of best quality wines from *Thompson seedless* grapes. Gallander⁴ and Suresh and Ethiraj⁵ have shown that intermediate maturity grapes produced best quality wines. Most of the varieties grown in dry temperate regions of Himachal Pradesh were introduced by foreign missionaries, and they mainly belong to *Labrusca* group or its hybrids with *Vinifera* and occupy about 90 per cent of the area under grapes⁶

There has been considerable work on factors affecting the yield and quality of juice and wine abroad but very little information is available for grapes grown under dry temperate climatic conditions. Hence, the present investigation was undertaken to study the effect of fruit maturity on the yield, composition and quality of juice, and wine from grapes.

Materials and Methods

Two exotic (*Thompson Seedless* and *Anab-e-Shahi*) and three local cultivars (*Chholtu Red*, *Chholtu white*, and *Rangspay*) were procured from the Regional Horticultural Research Station, Sharbo, Himachal Pradesh. The berries were harvested at three different stages (at 10 d interval) of maturity, viz. early(H₁), intermediate (H₂), and late(H₃) during the month of August-September 1990 on the basis of their composition recorded in previous years. Bunch and berry weight was recorded by a sensitive balance, while the colour of the skin was recorded according to visual appearance. The specific gravity of berries was determined by water displacement method.

Juice was extracted from the sound berries (10 kg of each cultivar) after thorough washing and crushing in crusher and pressing in hand operated basket press. Crushed berries, prior to pressing were heated to 70 °C for 15 min to facilitate better colour extraction. The extracted hot juice was bottled, pasteurized for 20 min and used for wine preparation. Wine was prepared by inoculating the juice with 5 per cent active culture of *Saccharomyces cerevisiae* which was prepared in sterilized juice. Fermentation was

carried out at 22 ± 1 °C in glass containers using cotton plugs. After reaching dryness (4–6°B), the wine was racked and treated with 25 ppm of sulphur dioxide. The clarified wine was bottled and analysed for various physico-chemical and sensory parameters.

Standard analytical procedures were followed for determination of various physico-chemical properties of juice and wine. Rate of the fermentation was estimated as fall in °B/24 h. The TSS of the juice was measured by a hand refractometer⁷. Titratable acidity was estimated as tartaric acid and acetic acid as described earlier^{7,8}. The pH value was determined with the help of digital pH meter⁹ (Systronic model 324). Sugars (reducing and total) were estimated by Lane and Eynon's volumetric method¹⁰. Tannins as tannic acid were estimated according to the method described by AOAC¹⁰. The alcohol content was determined as per the standard method of Amerine and Ough⁸. Sensory evaluation of the juice and wine was carried out for colour, flavour, taste and overall acceptability by a panel comprising seven semi-trained panelists using a nine-point hedonic scale⁹. The data were analysed statistically using factorial RBD with three replications and means were compared at 5 per cent level of significance¹¹.

Results and Discussion

Physico-chemical analysis of different varieties (Table 1) at three stages of maturity indicated that as the maturity advanced, berry weight, bunch weight, specific gravity, total soluble solids, pH, sugars, TSS/acid ratio increased with a corresponding decrease in acidity and tannins. Change in colour of different varieties was noticed with the advancement in maturity. Variation in number of days from full bloom to harvest was observed in all the cultivars except for *Chholtu Red* and *Chholtu white*, where these were the same. The recovery of juice was comparatively higher in exotic cultivars and varied with maturity in all the cultivars. The sensory panel (Table 2) rated the colour, flavour and taste of juices from H₃ grapes to be higher as compared to the flavour of H₁ and H₂. A better taste of exotic cultivars at intermediate maturity (H₂ stage) resulted in better acceptability of their juice. However, the juice from three local cultivars was found to have good taste at the last stage of maturity (H₃) but, it was unaccept-

able as pure juice due to high astringency. On the other hand, the juice of exotic cultivars (H₁ stage) and local cultivars (H₁ and H₂ stage) were too acidic, and thus, the flavour and taste of these juices was rated unacceptable. In general, the acceptability of juices is influenced by the taste. The optimum total soluble solids/acid ratio of exotic cultivars ranged between 27 and 36, whereas the ratio for local cultivars ranged between 23 and 35. Flora¹² has reported the soluble solids/acid ratio of 25 to 35 to be optimum for muscadine grape juice. However, Gallander⁴ has reported that the °Brix/acid ratios for optimum harvesting in cooler regions are considerably lower than those recommended for warm climatic regions.

The physico-chemical composition and sensory score of wines are presented in Table 3. The fermentation rate was slow in wines from less mature grapes. The rate of fermentation increased as the sugar content in berries increased. The slow rate of fermentation may be due to imbalance in assimilable nitrogen and sugar contents of the must. Wines of different cultivars from more mature grapes (H₃ stage) gave higher yield of alcohol. The highest alcohol content of 10.26 per cent was found in *Thompson Seedless* variety at H₃ stage of harvest. The alcohol content of wine from different varieties varied between 4.92 and 10.26 per cent, indicating that except *Thompson Seedless* all the other cultivars could not yield good amount of alcohol and need to be ameliorated with sugar. The total acidity and tannins in wines decreased while pH increased as compared to juice after fermentation. The decrease in total acidity may be due to the precipitation of acids and tannins during fermentation and racking. Kundu *et al*¹³ have also reported the decrease in acids and tannins during ageing of wines. Volatile acidity of different wines ranged between 0.020 and 0.038 per cent indicating that wine from more mature berries had more volatile acids. The sensory evaluation scores indicated that intermediate maturity (H₂ stage) grapes of exotic cultivars produced acceptable wine as compared to early harvested (H₁ stage) one. Sensory score of wine from exotic cultivars further increased at late harvest (H₃ stage). On the other hand, local cultivars produced acceptable wine only from late harvested berries (H₃ stage). The increased sensory score of wine from mature grapes may be due to proper balance of aroma, acid, and overall quality.

Table 1 — Physico-chemical composition of grapes

Variety	Harvesting stage	Berry weight, g	Bunch weight, g	Specific gravity	Days from full bloom to harvest	Colour of berries	Total soluble solids, per cent	Acidity, (per cent, tartaric acid)	pH	Reducing sugars, per cent	Total sugars, per cent	TSS/acid ratio	Tannins (mg/100g)
<i>Thompson Seedless</i>	H ₁	1.95 ^c	336 ^d	0.96 ^c	86	Greenish yellow	22.0 ^c	0.75 ^b	3.22 ^c	17.4 ^c	20.1 ^{bc}	29.3	28.6 ^h
	H ₂	2.33 ^c	370 ^c	0.97 ^c	96	Light yellow	23.0 ^{bc}	0.64 ^b	3.28 ^c	20.0 ^b	22.2 ^{ab}	35.9	27.06 ^h
	H ₃	2.44 ^c	384 ^{bc}	0.99 ^{bc}	106	Light to deep yellow	24.9 ^a	0.58 ^b	3.28 ^c	22.2 ^a	23.2 ^a	42.9	26.24 ^h
<i>Anab-e-shahi</i>	H ₁	7.33 ^a	404 ^b	0.98 ^b	90	Light green	14.0 ^g	0.62 ^b	3.37 ^{bc}	11.8 ^b	13.1 ^f	22.5	19.72
	H ₂	8.00 ^a	533 ^a	1.03 ^{ab}	100	White	15.5 ^g	0.57 ^b	3.52 ^{ab}	12.9 ^b	14.7 ^a	27.6	17.25 ⁱ
	H ₃	8.17 ^a	545 ^a	1.03 ^{ab}	110	White to light yellow	17.0 ^{ef}	0.47 ^b	3.65 ^a	14.6 ^{de}	15.8 ^{de}	36.2	16.6 ⁱ
<i>Chholti Red</i>	H ₁	2.43 ^c	220 ^f	1.01 ^b	91	Brown	17.0 ^{ef}	0.98 ^{ab}	2.88 ^c	13.8 ^c	14.3 ^c	17.3	132.38 ^b
	H ₂	2.60 ^c	233 ^f	1.03 ^{ab}	101	Red	19.4	0.80 ^b	2.98 ^{de}	15.4 ^d	17.7 ^d	24.2	120.60 ^d
	H ₃	2.67 ^c	238 ^{ef}	1.06 ^a	111	Dark Red	22.0	0.75 ^b	3.02 ^d	19.0 ^b	20.4 ^b	29.3	115.82 ^e
<i>Chholti White</i>	H ₁	3.0 ^b	253 ^e	1.05 ^a	91	Light green	14.6	0.66 ^b	3.26 ^c	12.5 ^f	13.0 ^f	22.1	138.36 ^e
	H ₂	3.33 ^b	258 ^e	1.05 ^a	101	Light yellow	16.5	0.56 ^b	3.31 ^c	12.9 ^{ef}	14.5 ^e	29.4	127.20 ^c
	H ₃	3.60 ^b	258 ^e	1.05 ^a	111	Light yellow	19.0	0.55 ^b	3.34 ^b	16.0 ^c	17.7 ^d	34.5	122.06 ^d
<i>Rangspay</i>	H ₁	1.76 ^d	395 ^b	1.03 ^a	88	Red	14.2	1.40 ^a	2.83 ^c	11.4 ^f	12.2 ^f	10.1	83.96 ^f
	H ₂	1.90 ^c	397 ^b	1.06 ^a	98	Reddish black	16.0	1.0 ^{ab}	3.10 ^d	12.5 ^{ef}	13.5 ^{ef}	16.0	78.03 ^g
	H ₃	1.94 ^c	405 ^b	1.06 ^a	108	Black	19.5	0.82 ^b	3.16 ^d	16.7 ^c	17.8 ^e	23.8	76.2 ^g
C D (0.05)		0.37	20.83	0.02	—	—	0.98	0.31	0.11	1.52	1.70	—	2.76
Variety (V)													
Harvesting stage (H)		0.33	15.97	0.01	—	—	0.76	0.13	0.09	0.74	0.83	—	2.29
VxH		0.86	23.06	0.04	—	—	1.36	0.54	0.20	2.08	2.39	—	3.98

In a column means followed by a common alphabet are not significantly different at 5 per cent level

Table 2 — Juice yield and scores for various sensory characteristics of grapes

Variety	Harvesting date	Juice recovery, per cent	Sensory attribute				Remarks
			Colour	Flavour	Taste	Overall acceptability	
<i>Thompson Seedless</i>	H ₁	75.0 ^e	4.8 ^e	5.0 ^{ef}	5.3 ^{de}	5.03 ^c	Sugar acid blend fair, not acceptable
	H ₂	77.5 ^{cd}	6.9 ^d	7.2 ^{bc}	7.9 ^a	7.33 ^a	Colour, flavour and sugar/acid blend good, acceptable
	H ₃	78.2 ^c	7.8 ^{bc}	8.0 ^d	8.2 ^a	8.0 ^a	Colour, flavour and sugar/acid blend good, acceptable
<i>Anab-e-Shahi</i>	H ₁	76.7 ^d	5.4 ^f	4.6 ^f	5.0 ^e	5.0 ^{cd}	Sugar/acid blend poor, greenish in colour, not acceptable
	H ₂	80.0 ^b	7.0 ^d	7.2 ^{bc}	7.5 ^{ab}	7.23 ^a	Dull yellowish in colour, sugar/ acid blend good, acceptable
	H ₃	81.4 ^b	8.2 ^{ab}	7.5 ^b	7.8 ^a	7.83 ^a	Sugar/ acid blend best, reddish yellow in colour, acceptable
<i>Chholu Red</i>	H ₁	68.8 ^a	4.8 ^f	3.2 ^{gh}	2.5 ^g	3.5 ^{cd}	Poor sugar/acid blend, astringent, not acceptable
	H ₂	70.2 ^h	6.8 ^d	6.2 ^d	5.7 ^d	6.23 ^b	Sugar/acid blend fair, astringent, red in colour but not acceptable
	H ₃	73.4 ^g	8.2 ^{ab}	7.0 ^e	6.6 ^e	7.27 ^a	Brick red in colour, sugar/acid blend good, unacceptable as juice
<i>Chholu White</i>	H ₁	73.8 ^{fg}	4.0 ^g	2.8 ^h	2.6 ^g	3.13 ^f	Astringent, sugar/acid blend poor, brown colour, not acceptable
	H ₂	74.5 ^{ef}	7.2 ^{cd}	6.8 ^c	4.1 ^f	6.03 ^b	Sugar/acid blend fair, astringent, reddish brown, not acceptable
	H ₃	75.0 ^e	8.5 ^c	7.6 ^{ab}	7.0 ^{bc}	7.70 ^a	Sugar/acid blend good but astringent, yellowish red but not acceptable
<i>Rangspay</i>	H ₁	73.0 ^g	6.2 ^e	3.5 ^g	3.6 ^b	4.43 ^{de}	Highly acidic, red in colour, not acceptable as pure juice
	H ₂	73.8 ^{fg}	7.8 ^{bc}	5.3 ^e	4.0 ^f	5.70 ^{bc}	Sugar/acid blend fair, red in colour, astringent, not acceptable
	H ₃	75.0 ^c	8.6 ^a	8.0 ^a	6.0 ^{cd}	7.53 ^a	Sugar/acid blend good, astringent, deep red in colour, not acceptable as pure juice
C D (0.05) Variety (V)		0.66	0.42	0.26	0.57	0.76	
Harvesting stage (H)		0.49	0.35	0.22	0.48	0.62	
VxH		0.88	0.69	0.47	0.73	0.99	

In a column means followed by a common alphabet are not significantly different at 5 per cent level

Table 3 — Physico-chemical and sensory characteristics of wine

Variety	Harvesting stage	Alcohol per cent (v/v)	Total acidity (per cent, tartaric acid)	pH	Volatile acidity (per cent, acetic acid)	Tannins (mg/100g)	Rate of fermentation	Overall acceptability
<i>Thompson Seed- less</i>	H ₁	8.64 ^{bc}	0.72 ^d	3.27 ^b	0.021 ^c	23.06 ^f	1.44 ^a	4.68 ^f
	H ₂	9.24 ^b	0.58 ^f	3.25 ^{bc}	0.033 ^a	20.18 ^{fg}	1.54 ^a	7.20 ^{bc}
	H ₃	10.26 ^a	0.56 ^g	3.30 ^{bc}	0.038 ^a	16.74 ^g	1.71 ^a	8.68 ^a
<i>Anab-e-Shahi</i>	H ₁	5.10 ^j	0.62 ^e	3.40 ^b	0.020 ^c	17.46 ^g	0.85 ^{bc}	4.88 ^{ef}
	H ₂	5.82 ⁱ	0.56 ^g	3.60 ^a	0.026 ^b	15.09 ^h	0.97 ^b	7.00 ^{cd}
	H ₃	6.72 ^g	0.50 ⁱ	3.60 ^a	0.024 ^{bc}	11.62 ^h	1.12 ^b	7.52 ^b
<i>Chholti Red</i>	H ₁	6.24 ^f	0.96 ^b	2.90 ^d	0.030 ^b	130.00 ^a	1.04 ^b	3.76 ^{fg}
	H ₂	7.80 ^a	0.76 ^c	3.05 ^d	0.032 ^a	112.12 ^b	1.30 ^{ab}	6.00 ^d
	H ₃	8.4 ^d	0.74 ^c	3.15 ^{cd}	0.035 ^a	101.26 ^c	1.40 ^a	7.58 ^{ab}
<i>Chholti White</i>	H ₁	5.34 ^j	0.63 ^e	3.26 ^{bc}	0.024 ^b	130.46 ^a	0.89 ^b	3.06 ^g
	H ₂	6.34 ^h	0.58 ^f	3.30 ^{bc}	0.031 ^{ab}	110.55 ^b	1.06 ^b	6.00 ^d
	H ₃	7.26 ^e	0.52 ^h	3.41 ^b	0.031 ^{ab}	105.10 ^c	1.21 ^b	7.62 ^a
<i>Rangspay</i>	H ₁	4.92 ^j	1.22 ^a	2.92 ^d	0.026 ^b	80.00 ^d	0.82 ^c	4.68 ^f
	H ₂	6.00 ^h	0.98 ^b	3.05 ^b	0.033 ^a	71.72 ^e	1.00 ^b	5.96 ^{de}
	H ₃	7.2 ^{ef}	0.75 ^c	3.20 ^c	0.030 ^b	68.75 ^e	1.20 ^b	7.50 ^b
C D (0.05)		0.40	0.08	0.11	0.005	3.66	0.26	0.87
Variety (V)								
Harvesting stage (H)		0.34	0.07	0.10	0.003	2.87	0.22	0.65
VxH		0.69	0.13	0.19	0.007	5.05	0.45	1.12

In a column means followed by a common alphabet are not significantly different at 5 per cent level

Conclusions

It is concluded that the exotic cultivars should be harvested at intermediate (H_2 stage) maturity for the production of acceptable juice and wine, while local cultivars are unsuitable for production of pure juice at any stage of harvest but can be successfully utilized for the production of acceptable Red Wine at late maturity (H_3 stage).

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Bitterants As Denaturants for Industrial Alcohol

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Brucine, bitrex (Denatonium Benzoate) and amerex (Denatonium Saccharide) have been studied as denaturants for industrial alcohol. In order to render ordinary denatured spirit (ODS)/specially denatured spirit (SDS) adversely bitter even at the potable dilution (20% v/v) of alcohol, the following concentrations of bitterants were found suitable: brucine or brucine sulphate 200 ppm, bitrex 100 ppm and amerex 50 ppm in ODS/SDS respectively. The above bitterants were assayed by UV spectrophotometry at λ 264 nm.

Introduction

Since primitive days, alcohol is being used as a stimulating beverage by man to overcome his agonies and has also found innumerable uses in industries mainly as a solvent. Large quantities of such alcohol used in industries is rendered unfit for human consumption by denaturing it with additives like pyridine, coutchoucine¹, crotonaldehyde, etc. or with some special denaturants like benzene, acetone, ethylacetate, etc. and is called ODS/SDS.

From time to time liquor tragedies have taken toll of innocent lives as methyl alcohol is added to it. This has initiated the 'Denaturant Committee' to take some preventive measures to curb the recurrence of such incidents. Colouring of alcohol may warn the user but its removal may be troublesome for industries as it will involve another process to eliminate the colour. Also, a bitterant additive is definitely sufficient to warn the user, but a bitterant at low concentration may be enjoyable. Therefore, a series of experiments have been undertaken using different bitterants like brucine², bitrex² and amerex, determining their bitterness at ppm level concentrations in potable dilution of ODS/SDS (20% of alcohol), cost involved for addition/removal if necessary, and threshold level concentration of the bitterants by sensory evaluation (tasted by three to four persons).

Materials and Methods

Brucine (purity 99%) was obtained from Loba Chemic. Pvt Ltd, Mumbai. Different concentrations of brucine were tried for bitterness taste and the minimum concentration of the bitterant was found to be with 200 ppm (200 mg/l). Upon five-fold dilution, potable strength (20% v/v of alcohol) containing 40 ppm level of brucine in ODS/SDS was obtained. The removal of bitterness was done by boiling for one minute with activated charcoal and then filtering by Whatman No.1 filter paper. The solution was tested for total removal of bitterness by tongue taste. The amount of activated charcoal for removing bitterness was 2 gm/l.

Bitrex (Denatinium Benzoate) was imported from Macfarlan Smith Ltd, Edinburgh through G. Loucatos and Co., Mumbai. Different concentrations of bitrex were tried for bitterness taste and the minimum concentration for bitterness was found to be 100 ppm (100 mg/l) in ODS/SDS. Upon five-fold dilution, potable strength (20% v/v) of alcohol containing 20 ppm level of bitrex in ODS/SDS was obtained. The removal of bitrex could be achieved by activated charcoal (2 gm/l).

Amerex (Denatonium Saccharide) was obtained from United Phosphorous Ltd. The potable concentration of amerex for bitterness in taste was found to be 50 ppm (50 mg/l) in ODS/SDS. Upon five-fold dilution for producing potable strength (20% v/v of alcohol), amerex level was 10 ppm in ODS/SDS. The

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removal of bitterness could be achieved by activated charcoal 2 gm/l.

Results and Discussion

Threshold level concentration of these bitterants was determined by sensory evaluation of serial dilutions by three/four persons. The samples were tasted so that at the lowest level the bitterness could be maintained which was not enjoyable by the user. Brucine (40 ppm), bitrex (20 ppm) and amerex (10 ppm) level in ODS/SDS was found sufficiently bitter to dissuade the consumer from drinking.

The cost of the bitterants brucine, bitrex and amerex worked out to Rs 1.60, Rs 2.35 and Rs 0.1 respectively. The cost of import-duty paid bitrex is too high compared to more efficacious saccharide analogue manufactured indigenously. The bitterants at the above required concentrations could however, be removed efficiently from the five-fold diluted alcohol (20% v/v) potable strength by activated charcoal at the cost of Rs 0.25/l. (2 g activated charcoal/l). Quantitative analysis by UV spectrophotometry for brucine, bitrex and amerex was done. They all showed maximum absorption ($\lambda_{\max}$) at 264 nm at

10 ppm level in rectified spirit. For those industries requiring bitterants at lowest levels, amerex was found to be useful at even 10 ppm in SDS.

Brucine, bitrex and amerex are used normally for denaturing alcohol and oils, and in analytical chemistry for separating racemic mixtures³. Among the three bitterants, amerex is indigenously manufactured saccharide and proved to be more bitter even at 10 ppm level in SDS and found to be adversely bitter to dissuade the consumer from drinking. No denaturant at this low level is reported. The studies may help in eradicating the social menace that often grips the country resulting in great tragedies.

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BOOK REVIEWS

The US Paper Industry and Sustainable Production— An Argument for Restructuring, by Maureen Smith (The MIT Press, Cambridge, Mass. 02142-1399) 1997, pp 303, Price: \$ 30.00

The book on "The U S Paper Industry and Sustainable Production", written by Maureen Smith is an excellent attempt in bringing out the arguments and imperatives for restructuring the US pulp and paper industries from environmental point of views. All the relevant aspects such as resources, manufacturing processes, effluent qualities, recycling, government policies, public involvement, company reports and future prospects are readily available in this book. It critically examines the policies and perspective for the US paper industry *vis-a-vis* sustainable production. the TOCl (total organic halides) and AOX (adsorbable organic halides), generated in pulp production due to use of free Cl₂, having carcinogenic effect, have aroused ECF and TCF bleaching processes in the last decade. The seriousness of the issue has been reviewed.

The conception of sustainable development using recycled fibre already practiced in the US for more than a decade has been assessed. Wood and non-wood resources for pulp and paper as well as timber industries are included.

The book has general contents of pulp and paper manufacturing with an emphasis on environmental issues. While it may not be useful as a text book for pulp and paper technologists, it is quite useful for environmental policy-makers worldover. It has citations of many technical experts having economical consequences. It could have stressed, however, further why the issue of organochlorine is considered so important, namely from medical point of view, how many people have been reported so far to have died or have suffered in the US similar to that due to AIDS, etc. Such data could have made the issue noncontroversial which incidentally continues to persist. Conversion of existing manufacturing technologies leading to zero-discharge of carcinogenic

TOCl requires large investments. Some countries like Sweden, German, and Finland, have already accomplished in minimizing the AOX to the level of kg/tonne of pulp. In the US and Canada, many mills have been attempting to bring it down.

The book comprises six chapters which are as follows:

- 1 An Overview of the US Pulp and Paper Industry,
- 2 Forests and Fiber Resources,
- 3 Production Processes and Pollution,
- 4 Paper Recycling,
- 5 Case Study of An Urban Recycling Project, and
- 6 Prospects and Challenges.

Papermaking started in China in the first Century AD. We are now in fourth phase and according to the author, a fifth phase of sustainable production for 21st Century will arrive soon.

This book touches upon all types of mills; mini mills, greenfield mills, integrated, semi-integrated, unintegrated pulp, and paperboard mills, etc.

Discussion has been made on forests, timbers production, and wood utilization. The US paper industry has the largest consumption of wood in the country and largest industrial consumer of wood in the world. In 1991, total fibre used in domestic paper production was derived from pulpwood (45 per cent), wood residues (27 per cent), waste paper (28 per cent), nonwood fibres being negligible (1 per cent). Nonwood fibre resources such as wheat straw, corn stalks, and notably kenaf may be the future fibre resource.

Pollution has direct bearing on manufacturing processes. The two most important federal laws to define modern pollution control approach and its single medium orientation have been Clean Air Act (CCA), first passed in 1963; reauthorization and re-amendment in 1970 and then Clean Water Act (CWA) of 1972. Environmental Protection Agency (EPA), created in 1977, includes list of 126 toxic

"priority pollutants". Toxic Release Inventory (TRI) is to be performed.

Wood pulping technologies; such as Mechanical, Chemical, Bio- pulping and pulp bleaching with Cl_2 releases, PCDDs (polychlorinated dibenzo-*p*-dioxins) and PCPCs (polychlorinated phenolic compounds) are described in detail.

2, 3, 7, 8 - Tetra to octachloro dibenzene dioxins and furans have most serious effect. TCF, ECF, extended delignification, oxygen delignification, H_2O_2 , and ozone are discussed for zero furan production.

Use of pulp substitutes, newsprint, corrugated high grade deinking and mixed kraft paperboard, unbleached, bleached recycled paperboards urged in public enthusiasm for recycling in 1970s with suitable collection of waste paper.

Case Study of an Urban Recycling Project has been elaborated.

"The most daunting task facing those working to define the policies, strategies, and tools that can be used in the march toward more sustainable systems of production and consumption is the need to confront modern precepts of public planning, economics and economic development". The United States has been in industrial policy game most likely since 1643 when Massachusetts granted a new smelting company exclusive iron producing privileges.

The restructuring of industries for sustainable production has been well argued by the author in this book at the end.

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Industrialization, Inequality and Economic Growth, by Jeffrey G Williamson (Edward Elgar Publishing Limited, Cheltenham, Glos, GL50 2HU, UK) 1997, pp 312, Price: £ 49.95
[ISBN 185898 396 7 (hb)]

This is an interesting book on economic development with a different approach. The contemporary establishment economists are mostly concerned with macroeconomics and structural reforms. For many persons, rate of economic growth and world trade parameters are often the only key indicators to be followed. The performance of the Eastern tigers and China are often quoted as examples. On the other hand, those concerned with non-economic human

value considerations are often carried away with the issues presently articulated in the developed world: global warming; child labour; quality of life, ecology, etc.

Practical persons concerned with implementation and execution, especially in countries like India, are baffled with variety of problems they have to face. Whether it is an administrator or business person or a technologist, one can instinctively feel the effect of the 'backlog' in development, in comparison with the developed world. How it was when Britain started the Industrial revolution; or America grew or Japan started the 'catch up'— is a question that comes to one's mind.

This book through its eleven researched essays written between 1977 and 1994 provides an informed picture of the past. There are copious references. As the author states in the introduction "All of the essays included in this book deal with economic history, but with the agenda in each one explicitly moulded by contemporary debate about Third world development. The questions were posed that way on purpose since I wanted then, as I still do, to use history to speak to these Third World debates..... I believe that Third World analysts ignore economic history at their peril.....".

The essays are well written but require a good grounding in economics to understand the arguments. For example the first essay is based on analyses of detailed data about the "conventional" sources of growth accounting in Japan during 1887- 1988, basically the Meiji and Taisho history. The aim is to infer conjectures as to the extent developing countries can draw their "lessons". The authors come to many different, if not startling, conclusions: While growth versus equity conflicts are central to conventional development models, they fail in Japanese postwar case. For a century of Japanese savings and accumulation, the declining relative price of capital goods plays a significant, positive role throughout. The authors also conclude that in the conventional literature, policy experimentation by Meiji and Taisho leaders receives prime attention, but the extraordinary advantage of weak "population pressure" is hardly noted. And the government had no population policy! Also Meiji Japan's military adventurism did not retard development and helped in private capital formation, albeit through the Japanese luck of

indemnities won. There are many such conclusions, providing a complex picture of Japanese growth model as against simplistic theories.

The second chapter discusses the Kuznets curve, in the context of nineteenth century America, Kuznets postulated that modern economic growth inevitably fostered inequality. By decomposing the sources of rising capital-formation and net investment rates, the author shows that increased inequality did not account for significant portions of increased saving rates and foreign capital never offered an easy means of accelerating accumulation performance either. Inequality may have been a byproduct of modern economic growth but modern economic growth was not dependent upon increased inequality. He emphasizes attention to the endogenous influences of unbalanced rates of total factor productivity.

There are several chapters devoted to the study of British growth rates, starting from Industrial revolution; living standards of English workers, etc. A detailed analysis shows that Industrial Revolution was not really revolution but very slow in the initial years in terms of capital formation. Among other reasons the wars turn out to be a reason. There are interesting conclusions about migration from villages to cities.

British growth of cities is discussed in a chapter. At the beginning the author describes the Third World problems of fast growth of cities, persistent influx of rural emigrants, densely packed slums, the lowering quality of the city environment, etc. And then goes on to state "None of this would sound unfamiliar to Victorians coping with city growth in the middle third of the nineteenth century. They too were overwhelmed by the same 'success' and they did not have World Bank and foreign technologies to help them cope (the emphasis added by the reviewer). They too took innumerable surveys, held countless parliamentary hearings, published one official document or another, searched for scapegoats and struggled with reform". After considerable discussion of analysed data, mortality rates, wage labour, etc., ends the essay with the question, "Did the unfortunate environmental ugliness of (19th century) Britain's cities reflect, nonetheless an efficient path to industrialization? We simply do not know".

The book is remarkable because the essays attempt to question every theory and hypothesis prevalent. There is an attempt to decompose various elements to identify more closely the cause-and-effect interactions, rather than be satisfied with macro-models. Not being professionally trained in economics, the reviewer is neither able to admire fully the beauty of analyses nor is in a position to critique them.

There was at first a feeling to give up writing a review. However, after going through many pages, it is recommended that scientists and technologists with deep interest in developmental issues should read this book. Some well versed in analyses may attempt similar analyses for India. Also attempt to place historically emergence of new scientific knowledge even in the UK, the US and Japanese contexts. Perhaps, it will show a newer dimension as yet unexplored.

A few overall messages emerge from the reading of the book: do not be carried away with simple one-shot-mantra to economic growth or development or human issues. Probably, there are no universal solutions or models either. Some of the analyses indicate that we are not alone in the problems faced. Another important message is that most solutions have been found internally or endogenously by Japan, the UK or the US.

On the whole, it is an enjoyable book even while one skips the details of analyses. The conclusions constantly remind a saying in the New Testament, Proverb 18:17: "*He who states his case first seems right until another comes to examine him*".

May be it applies to the conclusions of the book also.

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Economic Values and the Environment in the Developing World, by S Georgiou, D Whittington, D Pearce and D Moran (Edward Elgar Publishing Ltd, Cheltenham, Glos GL50 2HU, UK) 1997, pp x +167 Price: 39.95 (hb)
[ISBN 1 85898 500 5(hb)]

Environmental degradation has often gone hand in hand with development, indeed often it is proclaimed that the issues of development must take

precedence over environmental protection, since the two are not compatible. One of the greatest problems about protecting the environment is that in the currently dominant methodologies of economic appraisal, only man-made or modified goods are considered to have value, whereas nature and all her products are considered "Free Goods" which can be appropriated by anyone who has the power to do so. This enables policy makers to count irreversible depletion of the environment as income and growth, and allows industries to pass on the costs of pollution to future generations or to society, as a whole. This not only destroys the environment but poses intolerable burdens in terms of loss of livelihood to vulnerable sections of society which depend closely on the natural environment.

The first step in the path towards sustainable development is therefore the development of an accounting system to properly evaluate natural resources, so that they can bear scrutiny on the same terms as other factors in the economic system. There may be people who feel that this is a regressive step; they will argue that the natural environment has an intrinsic value that is superior to all economic considerations as the entire life of the planet depends on it, and that moral considerations are the best framework to consider questions of the environment. We may sympathize with this view, but power is overwhelmingly in the hands of those who look at everything strictly in terms of cash. In such a context, discussion of environmental protection in moralistic and intrinsic value terms will be counterproductive: conservation will be considered as foregoing the benefits of development. But if a language is developed in which conservation and protection of the environment are shown to have monetary value, then the views of the developer and conservationist become complementary to each other, rather than antagonistic. This will enormously strengthen the hands of those who fight for justice, equity and environmental sustainability.

But evaluating the environment in monetary terms is beset with many difficulties and complex considerations. First of all, the environment is a public good, and it is used jointly by society and no one can be excluded from it. Its benefits, current and future, are unpriced, since they are not participating in a market mechanism. It is then sought to compare such

unpriced assets with marketable, priced goods. Alternatively, the comparison may be between two unpriced assets, say air and water quality. Environmental economists try to get around this difficulty by imputing a value to the environment (or a specific function of the environment, e.g., absorption of pollution) in terms of finding a "Willingness to pay" (WTP) by individuals who are concerned. This they may find by direct questioning, or by indirect means such as property values near a pollution source as compared to one which is further away. Alternatively, there may be a "Willingness to accept" (WTA) compensation for environmental amenities foregone. In practice, of course, these may be flawed as indices of environmental value; in both WTP and WTA, the current generation has greater weightage than future generations, and the rich count for more than the poor. Also, intrinsic values and future option values are not easily captured by such techniques. But flawed as they are, environmental valuation techniques offer the only means of revealing the true costs of using up or polluting scarce natural resources or amenities. By monetizing the values, one can hope to make explicit the criteria that have been used to frame policy and to set up rational policies in taxation, licenses and permits, and compensating those who suffer due to some particular environmental problem. It will also help to choose between competing projects or alternate policies with differing environmental impacts.

The application of economic valuation methods is therefore one of deriving credible estimates of values in contexts of imperfect markets. For this very reason, it is of great importance in the context of the developing countries. Much of the danger of environmental degradation concerns the Third World; also much of the environment worth preserving, such as the rainforest or wetlands exist in Third World countries. Already there is a demand from the rich countries that the poor countries should restrict their industrial and economic growth in order to protect the environment; this is rightly rejected. Finding the right measures of value for natural systems might help to initiate a dialogue between the developed and the developing countries which could set the world onto a sustainable path.

The book under review is an important contribution to this area. In six brief chapters, the authors have introduced the concepts of economic evaluation of natural resources, explained the various methodologies involved, have presented nine different case studies in valuation from the developing countries using different techniques, and given guidelines for the utilisation of the various techniques. The last chapter is an extremely useful annotated bibliography comprising large number of references.

The first chapter, after introducing the concept and arguing the need for natural resources evaluation, discusses the various components of it such as direct use value, indirect use value, option value and intrinsic value. The importance of natural resources accounting in national and sectoral policies in the developing countries is pointed out, and some means of countering the inherent bias in the WTP approach by means of equity weightages is discussed.

The second chapter discusses the different methods in depth. Both direct methods (answers elicited through questionnaires) and indirect methods (values estimated through observed economic behavior) are presented. Among the direct methods are contingent valuation, contingent ranking, and conjoint analysis. The indirect methods discussed consist of both conventional market (dose-response, replacement costs) and surrogate markets (hedonic pricing, travel cost, random utility model, 'averting behaviour' model). Some methods of reducing biases and increasing reliability in the application of these models are also discussed.

The core of the book is perhaps the third chapter, which presents case studies from the developing countries. Both direct and indirect valuation techniques are used. Contingent valuation method is used for evaluating water quality in Philippines, Uruguay, and Barbados, and for improved sanitation in Ghana. Production function analysis is used for analysing health costs of air pollution in Brazil, protection of rain forest in Cameroon, and for afforestation benefits in Nigeria. A random utility model is used for evaluating water supply provision in Pakistan, and hedonic pricing method for doing the same in Philippines, thus demonstrating applicability and constraints in using different methods. An opportunity cost analysis is used along with contingent valuation for analysing forest preservation in Madagascar. A

travel cost method is used for analysing the value of eco-tourism in a rain forest preserve in Costa Rica. The case studies demonstrate that the methods of environmental monetization are applicable in developing country contexts. The water supply, water quality and sanitation studies suggest that people are willing to pay reasonably for improved environmental and public health facilities, and that they would be able to pay for the construction of most sanitation and water supply facilities if long term credit is made available at interest rates prevailing in most of the advanced countries. What prevents such developments in most developing countries is the sheer unavailability of credit on reasonable terms, and the lack of corruption free administration of construction and long term use. So here is an important result which can be used in planning and in international aid.

The next two chapters deal with the applicability of the techniques and on how to deal with some of the problems encountered. Emphasis is laid on presenting the results in a form immediately usable by the client. Among the difficulties mentioned are data problems, the identification of realistic and validated discount rates, and overall costs of the study. The need for training researchers is also touched upon.

The last chapter is an annotated reference list of various areas of importance for environmentalists. The list is quite extensive, and includes most of the major problem areas such as biodiversity, climate change, forests, coastal areas, and wetlands. Human related issues such as health, sanitation, water supply and water quality, solid waste management are also discussed.

The book has succeeded in demonstrating the utility of environmental evaluation techniques in the context of the developing countries in a clear and concise manner. There are a few problem areas, for instance, on how to account for differences in purchasing power between tourists and local people in valuating eco-tourism. But such difficulties can be solved. It is hoped that environmental evaluation techniques will become an integral part of developmental planning.

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SCI-TECH UPDATE

Smart cards technology benefits for banking, health and transport sectors

Scientists from the TNO Centre for Technology and Policy Studies and the TNO Institute of Infrastructure, Transport and Regional Development have identified three main areas where smart cards are likely to make significant contribution, viz., (i) banking and the retail sector; (ii) health care; and (iii) traffic and transport.

TNO's Evaluation Centre for instrumentation and Security Techniques is engaged with digital and analogue electronics, chip architecture, cryptology and software design. To preserve its own identity and independence, the Centre has its own management, administrative services and quality systems. And as an extra precaution, the Centre operates an extremely strict security system in view of the confidential nature of its work. Most of its assignments are concerned with assessing the security aspects of bank cards, cheques and automatic teller machines, and even extend to evaluating complete computerized payment systems.

In the traditional application of smart cards in the banking and retail sector, it serves as an "electronic purse" to act as a good alternative to cash in a far more secure way.

In the health care sector, smart cards can play a major role in matters of life and death. When a patient is admitted in an emergency situation, the smart card can provide the doctors with vital information regarding a patient's medical records, e.g. his sensitivity to specific drugs, whether he is being treated for specific illness and the relevant details. Apart from this, the smart card can contain the family doctor's name, address, telephone number, etc.

Further plans are being taken up help specific groups of patients by using smart cards for working out precise treatment schedules including drug doses as in kidney sufferers.

In the transport sector, with the arrival of contactless smart cards, they have potential applications for controlling access to public system and for running road pricing schemes.

For controlling access to motorways and toll roads, long range contactless smart cards are better suited. These cards operate on radio signals and, for best results, should be prominently displayed on the vehicle's windscreen. Access to the network is controlled by a remote sensing unit positioned on a gantry above the road. As vehicles pass under the sensing point their owners' smart cards are debited automatically—which does away with the need for toll booths.

Smart card technology is also expected to be useful in harmonizing ticketing schemes and in helping enhance the efficiency of goods transport, by making bills of lading and delivery notes obsolete.

But TNO's work with smart cards is not confined to studying the implications of this exciting field of technology. There is also a lot of interesting work going on in the various TNO research laboratories. Apart from these applications, scientists at the TNO Physics and Electronics Laboratory are looking at the use of smart cards as sophisticated ID cards by storing biometric parameters, including voice prints, finger prints, retina scans, iris scans or dynamic signature patterns since these are always unique.

To gain access to a particular room or part of a building the user simply inserts his smart card in a smart card reader and this information is cross-checked with that supplied directly from his own voice, hand or eye.

TNO experts are currently assessing the use of biometric identifiers to control access to the Rotterdam container port. Before a driver is permitted to enter the site, his palm is scanned to check his identity.

Over the last few years, the Evaluation Centre for Instrumentation and Security Techniques, which forms part of the TNO Institute of Applied Physics, has assessed the suitability of some seventyfive dif-

ferent security systems, all of which make use of smart card technology [*TNO Mag*, Netherlands organization for Applied Scientific Research, 1 (1) (1997) 6-8]. □

DSRM

Infrared thermography to pinpoint flaws in radar enclosures

The on-board weather radar on aircraft has to work in accordance with some performance standards. The conical fibre glass enclosure on the aircrafts' nose which houses the radar is called radome and its manufacture and maintenance are of great importance.

For the efficient functioning, of the radar, the radome should provide at all times an electronically clear window through which the signal can be transmitted.

Moisture entrapped between the radome's laminates, or in its honey-comb or fluted core causes problems like delamination of it which will affect its structural integrity. Moreover, the entrapped moisture can block or deflect the radar signal passing through 6-12 mm radome's thin shell.

California Radomes (CR) a company which repairs radomes for commercial carriers, military and a number of corporate jet customers has invested in Thermovision thermal imaging camera from Agema Infrared Systems, New Jersey. The camera enables California Radome's crew to detect the presence of moisture and delaminations in the honeycomb-cored radome and to confirm that it was removed as well as to find out its cause.

The radome is heated up to 51.7°C for about 15 min and it is observed from all angles as it cools off. Trapped moisture and all the other defects will retain heat longer than the area around them and show up as 'hot spots'. With the thermal imaging camera, CR's staff claim that they could confirm the presence of moisture more accurately, isolate it more precisely and also identify other problems such as delaminations which was not possible earlier.

The radomes are brought for servicing to CR as a result of regular scheduled inspection at pre-specified intervals by the operators. Or they are presented for repair as a result of damage incurred in a hail storm, bird hit, ground accident or the like. It is stripped of all paint and subjected to an IR inspection as well as a 'tap' test, a moisture detector test and a

test to determine its transmissivity. Microwave beams of the appropriate 'X' or 'C' band are passed through the radome to determine the per cent of the radar signal passing through it.

Based on their testing, the inner or outer skin is removed to make the necessary repairs to the core structure of the radome. The skin(s) is (are) then replaced, the radome is sanded to ensure a smooth surface around the area of the patch and then repainted. An eddy current test is also performed to make sure that the radome thickness does not exceed the allowable tolerance specified. The repaired radome then receives one more IR inspection to ensure that all hot spots have been eliminated. Finally, the transmissivity test is repeated to ensure that there is no longer any significant loss or deflection of the radar signal [*INSIGHT*, 38 (11) (1996) 711]. □

DSRM

Internal combustion engine with a liquid piston

An ideal condition for the parts of an internal combustion engine is that they fit together tightly enough to stop hot gases seeping where they should not, and yet not so tightly that they rub on each other in a way that wears them out. This is the biggest challenge for design engineers.

One way to make gas-seals work perfectly is to use liquid pistons than solid ones. Fazle Hussain and Michael Goldshtik of the University of Houston (UOH) in Texas took up this rather fanciful concept and built a prototype of an engine with a liquid piston. Such a liquid piston can work only if its surface must be stable in the face of rapidly changing pressures.

In their prototype, the OUH team designed the piston to rotate. It has two cylinders and derives its power like a standards petrol engine by burning a mixture of fuel and air inside them. The difference is the compression required is achieved by what is in effect a thickening and thinning of the cylinder walls.

In the prototype used, water is tried as the liquid. Each of the cylinders has two slots in it. One admits liquid and one allows it to leave. And the outlet slot of each cylinder is connected to the inlet slot of the other by a channel. To start the engine, the liquid is injected under pressure into one of the cylinders. Because it is shot in at a tangent to the cylinder's inner wall, the water swirls around the cylinder and the resulting centrifugal force keeps it pressed close to the wall, thus stabilising its surface.

As more liquid is injected, the space at the centre of the cylinder shrinks, compressing the mixture of fuel and air that is inside it. Once this mixture is properly compressed, it is ignited by a spark plug. The resulting explosion then forces the liquid out of the exit slot and through the channel into the second cylinder. This means that as the space in one cylinder is expanding, the space in the other is contracting. Once the fuel-air mixture in the second cylinder is compressed enough, it too is sparked, forcing the fluid back into the first cylinder. With the assistance of some suitably-timed valves on the slots the liquid is forced repeatedly around the apparatus.

Dr Hussain achieves the driving effect by fitting each of the channels between the cylinders with a hydromotor—basically a small turbine. This could be attached to a drive-shaft in order to power a piece of machinery [*The Econ*, 5 April 1997, p. 80] □

DSRM

Improved automatic doser-mixer in food industry

Technology Stimulation Measures for SMEs (TSME) are implemented within the Fourth RTD Framework Programme of the EC and include ten research programmes.

Project CRAFT-1106 developed a reliable and automatic dose-mixer for using water in the food processing industry with gains on energy and production time.

Water used in the food and bread-making industries is required to be properly measured, controlled, controlled and mixed in right quantities and at right temperatures. Electronic dose-mixers used at present have the limitation of having a far too slow working velocity and consequently consume too much water and energy.

An Italian SME producing such equipment worked as a team with 3 of its clients and designed a fully automatic doser-mixer machine. The new design aimed at achieving fast and resistant temperature sensor, complex and reliable regulation system, digital and maintenance-free litre counter in an economical way.

The key element developed was an electronic temperature sensor that could resist different types of corrosion and have a faster response speed. The mixing of hot and cold water has been regulated by an electronic controlled mixing unit fitted with a

linear stepping actuator. The optimisation of the regulation was obtained through 'fuzzy' logic. Field testing of 30 successive prototypes allowed to overcome problems of design and noise. The team could manage to produce a conceptually simpler, reliable efficient prototype of with only one temperature sensor (instead of 3) and 2 valves instead of 4. The final prototype device will save on water and energy achieving a five-fold reduction in the water by-pass time (the amount of water lost before the nominal temperature is reached). The machine, further will have an improved reliability and requires less maintenance, thus increasing the time available for production by 20 to 30%.

Besides food industries, the machine and the mixing valve are expected to have a potential for exploitation in other areas such as the sanitary industry and large industrial installations [*Cordis Focus*, European Commission, Luxembourg, Suppl No 11, 29 October 1996, pp.10-11]. □

DSRM

New technology for recycling hazardous and non-hazardous wastes

A research team at the Waltham, Mass, USA has developed a molten metal technology called 'Catalytic Extraction Processing' (CEP). It converts wastes to products by dissolving a material to its component elements and then recovering the elements as useful raw material.

The conversion process involves injecting material into a molten metal bath. The catalytic properties of molten metal cause wastes to dissolve to their original elements thereby completely destroying any hazardous and toxic compounds. By controlling operating conditions and adding reactants, CEP rearranges the elements into high quality industrial gases, ceramic materials and metals.

In contrast to conventional treatment methods, CEP is a recycling technology that makes new products from wastes without releasing harmful emissions to the environment. Pollution can be prevented at the source itself through on-site integration of CEP systems at industrial facilities, allowing wastes and byproducts from manufacturing to be recycled rather than disposed off by burning or dumping. CEP processes organic and inorganic wastes in all physical forms: solids, liquid sludges, and gases. The initial target markets for CEP applications include commer-

cial radio- active waste generators, the chemical, petroleum, metals and commercial waste industries, and the government [*Environ Prog*, 15 (Fall 1996), (No.3) p.15]. □

HKK

Small scanner helps premature babies

Prof. David Edwards and his colleagues at the Hammersmith Hospital, London, have offered a better chance of survival and good health for premature babies with the introduction of a unique scanner into its intensive care unit.

This unique scanner is a scaled-down version of a giant magnetic resonance imaging and spectroscopy machine. The special scanner is only about 37 cm deep. Before the "shrunk" scanner was installed, babies had to be temporarily unhooked from their support tubes in the intensive care unit and taken to another part of the hospital.

The premature babies can undergo vital scanning within hours of birth, even when the child is wired up to machines that are helping immature lungs and heart to function.

Premature babies often have poor and immature lungs and insufficient hearts. The child can usually be scanned within a couple of hours of birth. Such scans can lead to early treatment to prevent possible permanent disability. The medical team has to know first is what is going on in a brain that has probably been damaged.

It is hoped that pictures obtained from the scanner will show when and how damage occurs and, when one uses treatments, whether one is succeeding or not. If a baby is starved of oxygen for some time then damage can occur, but there is a time lag of a few hours before this is irreversible, giving opportunity for treatment to prevent permanent disability.

There are no ethical questions about using the machine. It is totally non-invasive. No radiation, no injections, and surgery is required. The skin in any way is not punctured. The identification of brain damage at an early stage in a baby's life and the opportunity to learn how the brain develops will lead to new advances in treatment and a much brighter future for the child and its parents.

For further details, contact: Department of Paediatrics and Neonatal Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane

Road, London W12 ONN, UK; Fax: 181 740 8281. □

HKK

Unique chips utilize mobile protons

Researchers at the Sandia National Laboratories, Albuquerque, NM; France Telecom, Meylan Cedex, France; and the Defense Advanced Research Projects Agency, Arlington, Va. have designed a novel memory device that relies on protons rather than electrons to modulate voltage and current which may form the basis for a new type of integrated circuit technology.

The device performs on a par with existing technologies, requires fewer processing steps, and could operate at lower voltages than other semiconductor devices, all of which make it useful for industrial developments. The results are quite encouraging.

The researchers earlier determined that protons could be annealed into silicon dioxide (SiO_2) sandwiched between silicon films. There, the protons provide a way to help identify defective chips by modifying charge traps that inhibit semiconductor performance.

It was then discovered that the protons were mobile and thus might transport charge through the SiO_2 . By applying an electric field, they were able to control and rearrange the protons' space-charge distribution, as demonstrated by reversible voltage shifts at the Si/ SiO_2 interface. The protons presumably move around in SiO_2 by hopping from bridging oxygen to bridging oxygen.

The devices are quite robust, able to withstand heating to 200C and repeated voltage cycles without degradation.

In addition to this the activation energy required to set a proton in motion is only about 0.80V.

The protonic approach is one of many different advanced concepts that is being studied [*Chem Eng News*, 75(No.15)(1997) p.9]. □

HKK

Nanotubes wired for action

Rick Smalley *et al.* at the Rice University, Texas, in collaboration with Cees Dekker and his colleagues at the Dimes Institute of Delft University of Technology, The Netherlands, have developed a transistor fabricated from a single-wall carbon nanotube, an elongated 'whisker' of fullerene capped at both ends.

At only a single molecule in size, the new transistors not only approach the limits of miniaturization, but they are also expected to increase enormously the power of conventional silicon-based transistors (which are generally between 0.3 and 1 μm long).

The objective of developing molecular-based electronics has puzzled researchers for long. Until carbon nanotubes came along, one of the main difficulties in realising such devices was the problem of finding long and narrow molecules that could function as conductors. Unlike most other 'red-shaped' molecules, which are semiconductors or insulators, certain types of nanotubes do not undergo the so called Peierls transition, a tiny atomic rearrangement that leads to the opening of a Fermi energy gap, and can therefore behave as molecular wires.

Smalley and his group has devised a novel laser vapourisation method for synthesizing nanotubes in bulk to fabricate the resulting tubes as transistors in collaboration with Cees Dekker *et al.* of Delft University. Basically, their method involves using the nanotubes as a conducting wire by which to bridge two electrodes — source and drain contacts — for sending current through the device; a third gate electrode switches the device on and off. First, the electrodes — fine Pt strips — are produced by using electron beam lithography techniques, and then randomly super-impose the carbon nanotubes on top. An atomic force microscope allows them to pull out any devices where the nanotubes connect two of the Pt strips.

The resulting transistors work in a fundamentally different way from their silicon-based counter-parts. While conventional transistors rely on diffusive transport of electrons in doped semiconductors, single molecule versions operate according to the basic laws of quantum mechanism [*Chem Br*, 33 (6) (1997) p. 16; *Nature*, 386 (1997) p. 474]. □

HKK

Camera goes on smog patrol

NHK's Science & Technical Research Laboratories in Tokyo has developed a camera that can display infrared and ultraviolet light in real time and in colour, prior to this it could only be seen on the same screen if a computer merged and enhanced black-and-white images caught on separate cameras. This camera could be used for pollution monitoring, health checks and detecting art forgeries.

According to the member of the development team, Yoshihiko Ogaki, the camera has many advantages, only one camera was required to process both ultraviolet and infrared radiation instead of two and pictures were in colour, they did not require computer enhancement which saved time and money.

The camera could take in light between 250 and 1050 nanometres in wavelength. Light entering the camera split into three bands. Red to infrared waves, which comprised one band, pass through a charge-coupled device that compressed the electromagnetic radiation into visible light of wavelengths toward the red end of the visible spectrum.

For lengthening the wavelengths of ultraviolet radiation, the band of ultraviolet to blue waves passed to a device, the High-Gain Avalanche Rushing Amorphous Photoconductor (HARP), which brought it into the blue end of the spectrum.

After being converted into visible light, the two ends of the spectrum were then sent through a colour encoder along with the visible light to form a coherent image. To make the infrared and ultraviolet high stand out, the researchers represented them with shades rarely seen in real world objects [*New Scientist*, 154 (No. 2088) (1997) p. 19]. □

HSDK

Projections in growth of US polymer market up to 2001 AD

A study by Frost & Sullivan company describes that the sales of polymers, plastics and fine chemicals in the US grew from \$ 52.7 billion in 1994 to \$ 68 billion by the year 2001 AD, i.e. to say at a 4 per cent compound annual rate. In the same period, fine chemical's share of these combined markets will rise from 41 per cent in 1994 to 43 per cent in 2001 AD, while that of polymers and plastics correspondingly will dip from 59 to 57 per cent. Vendors offering the best price in the segments like medical products, additives for various industrial applications, including most catalysts, high-quality polyethylene and polypropylene materials and cosmetic and toiletry chemicals, may get annual growth of 10 to 20 per cent.

Asia and Eastern Europe emerged major suppliers for bulk active pharmaceuticals and similar fine chemical components. The US firms made huge investments in the Pacific Rim for producing polypropylene and polystyrene and these invest-

ments further increased. The developing countries are trying to provide high quality chemicals and plastics at prices much below those in the US and Europe.

Technological leadership is shared by half a dozen firms in Europe and about 20 in the US. In response to environmental concerns, water stability has become the basis for a wide array of products including paints and coatings. Plastics manufacturers have also responded with recycling campaigns. The development of value-added materials for lower-volume industry segments has come up recently. Mid-sized and smaller US based firms will not be able to keep up with the pace of technological advances in the near future and will be forced to wind up [*Chem Week*, 42 (No. 47) (1997) p. 123]. □

HSDK

Growth in industrial inorganic gases market linked to performance of chlor-alkali industry

According to Dr Angela Gunning of Frost and Sullivan, the demand and production of inorganic gases has increased due to recovery of the related industries, e.g. the ammonia manufacturing and fertilizers industry, chemical process industries, welding and metal processing and inert gas shielding and refrigeration. The European market for industrial inorganic gases is predicted to increase from prevailing \$ 13.34 billion to US \$ 19.44 billion by 2002 AD. The fastest growing sector is the air separation gases production having compound annual growth rate of 7.2 per cent for nitrogen and oxygen, 7 percent for argon, 6.7 per cent for carbon dioxide and 5.8 per cent for chlorine and hydrogen.

Survey made in 1995 showed that Germany was the largest European market of industrial inorganic gases with around 29.6 per cent of the market in terms of revenues. This is followed by Benelux countries (13.4 per cent), then France and Italy (11.6 per cent), the UK (11.4 per cent) followed by Scandinavia and Iberia. The largest six product segments of the market in terms of revenues were oxygen (29.9 per cent), chlorine (23.1 per cent), hydrogen (20.1 per cent), nitrogen (12.5 per cent), argon (10.6 per cent) and carbon dioxide (3.8 per cent).

For the base year 1995, the industrial inorganic gases distribution by unit shipments oxygen lead at 44.2 per cent, followed by nitrogen (28.2 per cent), then chlorine (19.8 per cent), carbon dioxide (4.3 per

cent), hydrogen (1.8 per cent) and argon (1.7 per cent). Companies which restructured their industrial activities during 1992-93 fared better than others. Companies dealing with medical or research gases were also successful.

The joint ventured companies got benefit from sharing distribution channels, R&D product registration and other costs. The manufacturing companies made efforts in reducing the discharges of wastewaters and the emissions of polluting gases. Most companies invested in environmental protection and the compliance with the proposed ISO14000 series of standards which regulate emissions and discharges in the environment and limits for various substances. For instance the Montreal Protocol which regulates the production and demand of CFCs had a strong impact on the chlor-alkali industry, which restructured and reoriented itself towards various products.

Technological changes were made during 1992-94 especially in chlor-alkali industry, manufacturing chlorine and hydrogen by replacing the mercury cell with the new membrane technology by most of the European chemical companies. As an example, new pressure-swing adsorption (PSA) technology and membrane separation units are used in the advanced purification and separation of air gases like nitrogen, oxygen and argon [*Chem Week*, 42 (No. 47) (1997) p. 122]. □

HSDK

Inexpensive new instant test for harmful *E. coli*

Certain toxic strains of *Escherichia Coli* produce toxins that cause intense and internal bleeding. At present no specific, convenient and simple test is available for routine examination to detect the bacteria. The tests used at present, use the sample for culturing for 24 or more hours after which the harmful organisms are detected with microscope or special dyes. Recent estimates have shown that *E. Coli* 0157:H7-the most common toxic *E. Coli* strain by far may be responsible for majority of illness. They may be present in anywhere from 0.1 to 3.7 percent of the raw meat sold in USA. These strains secrete a toxin that binds to a type of protein molecule, known as a receptor on the surface of the cells, that line the wall of the intestine. This toxin damages the cells and eventually leads to intestinal bleeding. It can then

enter the blood stream and in the most serious cases, damage the kidney.

Researchers at Lawrence Berkeley National Laboratory's Bio-molecular Materials Program have created an advanced thin-film bio-material that provides a fast and convenient test to detect the harmful bacteria analogous to a litmus test.

To build their detector, the researchers duplicated the intestinal cell-surface receptor molecule and joined it to an underlying "backbone" which is a long chain of linked lipid molecules that together constitute what is known as poly-diacetylene film which happens to be blue. But the binding of *E. Coli* toxin to the other part of the molecule (the cell surface receptor) breaks the links joining the lipids to one another changing the colour of the film to a reddish magenta.

The researchers say that most people can easily see the colour change triggered by *E. Coli* concentrations in the low parts-per-million range. If more sensitivity is required, a spectrophotometer can be used to detect the colour change, which is apt for use in a meat processing plant or some industrial environment.

The test film is reported to be made inexpensively which can be incorporated into packing materials and may soon become available commercially.

Meanwhile the Berkeley Group is exploring possibilities of using this test to detect almost any kind of harmful microbes from those in biological weapons to influenza virus [*Sci Am*, March 1997, p.36]. □

DSRM

Mobile imager to help cancer diagnosis

Prof. David Delpy and his team at the University College London, have developed a bedside near-infrared (NIR) light imager by the help of which the diagnosis of breast cancer and brain damage will be improved. The imager is completely mobile, which enables patients to be monitored at their bedside. In principle, local doctors could use the scanner in their surgeries and send the information electrically to a specialist for interpretation.

Significant advantage of NIR imaging over X-ray imaging is that it is harmless and thus can be used repeatedly or even continuously. NIR can also detect very small abnormalities and it is hoped that the scanner will show up tumours as small as 5 mm in

diam. It will prove suitable for scanning pre-menopausal women as well as post-menopausal subjects. The imager is also specially suitable for scanning the brain; it can identify damaged areas or early abnormalities in the brains of newborn babies.

For further information, contact:

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HKK

"Fat pill" reduces the body weight

Robert Dow *et al.* of the pharmaceuticals company Pfizer's laboratories in Groton, Connecticut have developed a drug that can make the body burn off calories without the need for excessive exercise. The molecule can boost the metabolism of rats by almost a one-third without increasing their appetites.

The molecule, called CP-331679, mimics one effect of adrenaline. This hormone binds to three types of receptors: one in the heart, which boosts the heart rate; another in blood vessels, which causes them to dilate; and the third on the surface of fat storage cells, which causes fats to be broken down for energy.

Dow and his colleagues targeted the third type, called beta-3 adrenergic receptors, reasoning that this would help to burn fat without affecting the cardiovascular system. The researchers tinkered with molecules known to stimulate adrenaline receptors until they came up with one that affected just the beta-3-receptors.

The molecule has not yet been tested in humans, but if its effects on rats were translated into human terms, people would shed just over a kilograms a week. However, human fats occur in different proportions to those of rats, which could limit the molecule's effect. The molecule works on the brown fat of rats, of which adult humans have very little.

It is stressed that overweight people will always need exercise and so drug should be considered a substitute for lifestyle changes. Merck of Rahway in New Jersey, e.g. has a beta-3 adrenergic stimulator under development [*New Sci*, 154 (No. 2079) (1997) p. 11]. □

HKK

New pill promises to prevent or treat flu

Gilead researchers along with those at the University of California, Berkeley, and the Australian National University, Canberra, are developing a pill that could prevent or treat all strains of influenza. The drug has completed animal tests successfully and is in for human trials. Named GS4104, the compound inhibits a key enzyme needed for replication of the flu virus in host cells.

To synthesize the new compound the teams have combined rational drug design with information derived from the crystal structure of known inhibitors bound to the target enzyme. One such inhibitor, zanamivir, produced by Glaxo Wellcome, is in Phase II clinical trials. However, it must be inhaled or used as a nasal spray.

Both the compounds inhibit neuraminidase, one of two proteins that cover the surface of the flu virus by binding to the enzyme's active site.

Neuraminidase works in concert with the second surface protein, hemagglutinin, to help the virus invade its host. Hemagglutinin binds to sugars called sialic acid that dot the surface of host cells, enabling the virus to enter. Neuraminidase, which cleaves sialic acid, is believed to play a dual role. It clears a path so that the flu virus can travel through mucous secretions in the respiratory tract, and it helps newly synthesized virus escape from infected cells to multiply. Both Glaxo's zanamivir and Gilead's GS4104 are sialic acid analogs.

In developing GS4104, Gilead *et al.* designed a new class of compounds containing a six-membered carbon ring in lieu of the dihydropyran ring in known neuraminidase inhibitors such as zanamivir. It was reasoned that a carbon ring would be chemically more stable and easier to modify to achieve optimum properties. Based on rational drug design, workers selected a cyclohexene ring scaffold as a transition-state analog.

After synthesizing the compound from quinic acid, they added alkane substituents to make drug candidates that were lipid-like and thus bio-available. Maximum neuraminidase inhibition was achieved with a pentyl group in the C-3 position. X-ray crystallographic studies of the inhibitor-neuraminidase complex suggest that the compound's antiviral potency is due to the interaction of the pentyl

group with a large hydrophobic pocket in the enzyme [*Chem Eng News*, **75** (No 5)(1997) p.14]. □

HKK

Report of the Working Groups of Information Society Forum of the European Commission

The European Commission decided to set up the Information Society Forum in February 1995 in order to create a new and authoritative source of reflection, debate and advice on the challenges of the Information Society.

The Forum consists of 128 members drawn from five main fields of activity:

- Users of the new technologies: industry (banks' retail, maritime etc), public services, consumer groups, small and medium-sized enterprises and the professions
- Social groups: academics, employers organisations and trade unions, youth groups, regional and city representatives
- Content and service providers: publishers and authors, film and TV producers, broadcasters, computer software producers and information service providers
- Network operators: fixed telecommunications, cable TV, mobile and satellite operators
- Institutions: members of Parliament, of the Economic and Social Committee of the Committee of the Regions and the data protection Commissioner.
- Six working groups have been formed whose members have given their views under the following heads:
 - the impact on the economy and employment;
 - basic social and democratic values in the "virtual community,"
 - the influence on public services
 - education, training and learning in the Information Society
 - the cultural dimension and the future of the media
 - sustainable development, technology and infrastructure

The European Commission has published the first Annual Report and the supplementary report (working group's reports) which can be obtained from the Information Society Forum Secretariat (European Commission, Information Society Activity Centre, 200 Rue de la Loi, BU 24, 2/70, B-1049 Brussels.

The full texts are also available on the ISPO web server at: URL: <http://www.ispo.cec.be/info-forum/pub.html>

Summary of the report of Working Group V under the head "The Cultural Dimension and the Future of the Media" is given in this issue. The other reports of the Working Groups will be covered in subsequent numbers of JSIR one in each issue.

Summary of Report of the Working Group V: The Culture Dimension and the Future of the Media.

During the first working year Working Group 5 has addressed the issues of the cultural dimension and the future of the media. The discussion was structured around four key topics, namely (1) technological convergence; (2) the profusion of distribution facilities; (3) intellectual property rights and (4) funding of the new communication systems. The following summary focusses on the main findings and the guiding principles identified.

The Cultural Challenge

The members embrace a broad definition of culture encompassing the sum of the behavioural patterns of society and not limited to "high culture" and the refined arts. The media which communicate this complex whole of a society's knowledge, customs and habits perpetuate, reinforce and spread culture in its broadest sense. This is why most members identify culture as an inseparable and pervasive elements of the media and the notion of the "Information Society".

New Information and communication technologies are going to change considerably the ways in which we presently produce and consume culture. They not only broaden the spectrum of information providers, they also support more distributed forms of organising information, giving rise to participatory forms of information production and distribution which some members have called "civic media". However, the full scope of the social and culture implications and the risks involved cannot as yet be fully understood. They need to be further examined.

Relevance and Consequences of Multimedia

Multimedia services are expected to play an increasingly important role both for the private and the professional lives of citizens. The specific qualities of "telespace" provide innovative tools for professional users, and they have the potential of also

enhancing the creativity and learning experience of each individual citizen. They also carry great potential for European industries and the European labour market. This is why Europe should ensure the proper market conditions for these services in order to reap all their benefits.

Multimedia services will satisfy a growing demand on the part of consumers to become actively involved in the exchange of information and data. At the same time, consumers will continue to demand and use traditional broadcasting services and print media on a large scale. These types of services complement rather than substitute for each other, much in the same way that theater, opera, books, magazines, newspapers, cinema, television, live concerts, radio and musical recordings today coexist with each other, each contributing to culture in their own way.

At the present stage, a high degree of uncertainty exists about possible ways of financing new services. The need for a return on investments will make online services, that may have been offered free of charge during an experimental phase, eventually more and more costly for consumers. Additional revenues may be generated through advertising. Even if the economic outlook of new services appears to be doubtful at present, members agree that as a general rule, there should be no public funding of commercially operated services. The market should determine the conditions for the success of these services.

Members also believe that public service broadcasters will continue to provide an important function in the culture and democratic traditions of their respective countries. Their public service mission including the active participation in the new technologies and services will be an essential element of the information society in order to ensure that all citizens will continue to have access to the full range of informational, educational, cultural, sports and entertainment programmes reflecting their respective societies as a whole as well as minority cultures at affordable costs for everyone. New services forming part of the public service mission need to be able to make use of the same kinds of public funding as traditional public broadcasting services. In addition, new models of public intervention of content creation may evolve to ensure plurality of content. Rights of access to the distribution systems

for public service programmes in keeping with their public service mission need to be safeguarded by "must-carry-rules".

Computer literacy is the first prerequisite for individuals to make use of and exploit the personal and professional possibilities that the new information technologies and services have to offer. This factor imposes a strong responsibility on the member states and the European Union to ensure a high standard of education in computer technologies for all European citizens and experiences with a participatory approach to the new media.

How to Strike the Regulatory Balance

A key issue for Europe's future in the information age is how to balance the need for viable information industries with the need to take into proper account that information is a unique good and service. There is a widespread belief among members that an effective regulatory framework is required.

1) to preserve and promote European cultures, in particular minority cultures, and to lend support to local initiatives in using the new media for expressing and developing their culture and building communities;

2) to safeguard competition on all levels of the information value chain, and to prevent the establishment of monopolistic positions, which can restrict pluralism and the free flow of information, services and programmes; such rules also need to address the phenomenon of vertical integration and should exempt public service broadcasters from media concentration rules;

3) to protect property rights in information transmitted via the networks;

4) to create chances for consumers to reap the benefits of the new media for the purpose of community building;

5) to safeguard non-discriminatory, fair transparent and reasonable rights of access for content providers to distribution and conditional access systems; to make market information gathered through control of infrastructure freely available to all content providers using the infrastructure; to address effectively the problem of "gatekeepers", and to ensure the fair and non-discriminatory design of navigational systems.

Members agree that the development of the information society cannot be left to the market forces alone. Where there are rules, the European Union and member states are called upon to apply these fairly across all relevant sectors, including traditional private media in both publishing and broadcasting. Also, while the universal service concept is regarded by many as an evolving and dynamic concept, members argue in favour of keeping this concept separate from the public service concept of broadcasting.

Another important regulatory issue concerns intellectual property rights (IPR). This has been the most controversial subject of the Working Group. Consequently, no final conclusions and recommendations have emerged so far. However, members agree that the legal regime governing IPR should ensure that creativity be rewarded adequately in economic terms. They also argue in favour of a balanced approach between authors' rights, publishers' right and the rights of users adequately to exploit IPRs in the context of digital transmission and multimedia.

Two different approaches to new IPR legislation have been advanced concerning the question of whom the principal economic benefits of IPR should go to:

1) One group of members supports the Continental European model of "droit d'auteurs", including its notion of moral rights, which vests intellectual property rights in the authors and holders of related rights.

2) Another group of members has spoken out in favour of the Anglo-American system of copyright law, which vests intellectual property rights in the producer [First Annual Report to the European Commission from the Information Society Forum Secretariat, European Commission, Information Society Activity Centre, 200 Rue de la Loi, BU 24, 2/70, B-1049 Brussels].

Announcements

Environment India '98

A four-day exhibition and conference on environment to focus on "clean technology makes good business sense" and on the fact that choice of technology plays a critical role in improving the production efficiency and in reducing waste/pollution is to be organized by Exhibitions India during March 31 - April 3, 1998. An International film festival focussing on the environment will be held concurrently.

The Asian Development Bank report on Asia's environment showed that (1) Out of the world's 15 most polluted cities, 13 were in Asia, (2) At least 1 in 3 Asians still does not have access to safe drinking water and (3) At least 1 in 2 has no access to sanitation. India, very much a part of this environment crisis, is sagging under the pressure of increasing population and continuing environment degradation.

This alarming scenario has created an explosive situation where solutions to the environment problems are being sought, found and marketed. India is potentially a vast market for manufacturing and suppliers of waste and pollution control equipment, water and waste water management, recycling etc.

Environment India '98, focussing on this, is co-sponsored by the Ministry of Environment and Forests, the Ministry of Water Resources, Central Pollution Control Board (CPCB), the Centre for Science & Environment (CSE), the National Productivity Council (NPC), the Tata Energy Research Institute (TERI) and the United Nations Development Programme (UNDP).

Further details may be obtained from:
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Placement Service in Food Processing Industries

Centre for Processed Foods (CPF), Bangalore, India, a non-profit, non-government organisation with a mission to work towards the development of a strong and modern food processing industry are pleased to provide placement services for professionals at various levels (Fresher, Junior level, Middle level, Senior Executives and very Senior Executives) in food processing industries. Confidentiality will be strictly maintained.

Individuals and industries who wish to utilize this service may contact:

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Journal of Scientific & Industrial Research

(Incorporating *Research and Industry*)

Instructions to Contributors

The **Journal of Scientific & Industrial Research** (Incorporating *Research and Industry*) is published monthly to serve as an information link between the generators and users of technologies. It is addressed primarily to industrial entrepreneurs, technologists, engineers, technocrats and administrators in industry. Therefore, original research articles of practical interest to industry are invited for publication.

Contributions should have an economic bias, and wherever possible, cost estimates should be provided. They should be tersely written, giving only the significant results.

Besides, reviews on various branches of science and technology, science/industrial policy and management are also accepted.

Subject Coverage

Scientific Industrial Research

- (i) Scientific investigations successful at the pilot-plant and in-plant trials.
- (ii) Technology upgradation.
- (iii) Development of cheaper and indigenous raw materials as replacement for uneconomical materials.
- (iiv) Import substitution.
- (v) Technologies for rural development.
- (vi) Standardization and quality control.
- (vii) Technologies of waste management.
- (viii) Industrial R&D highlights.

Technology Management

- (i) Success/failure stories in technology management.
- (ii) Technology assessment.

(iii) Technology transfer.

(iv) Technology assimilation and adaption in different industries.

(v) Technology funding including venture capital.

(vi) Human Resource Development.

vii) Management.

(viii) Environmental management.

Industrial Development

- (i) Policies, programmes and progress.
- (ii) Critical profiles of industries—individual and sectoral.
- (iii) Technology Forecasting .
- (iv) International Collaboration.
- (v) Fiscal incentives aimed at industrial development.

Books, monographs and technical bulletins on industrial methods and techniques as well as other data like production and demand statistics are accepted for review.

A critical analysis of papers presented at any Indian as well as international technology seminar/symposium is also welcome.

Questions on the articles published in the journal, answers supplementing any of the published items, views, opinions, or suggestions on the various aspects of technology are welcome for inclusion in the column, 'readers react'.

The editors are keen in projecting the technology bottlenecks/problems faced by the industry for their solution by the scientists in various laboratories. They would welcome to be mediators between the industry and the laboratory.

Preparation of Manuscript

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The discussion should deal with the interpretation of results. It should relate the new findings to the known, and include logical deductions.

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For names of periodicals, the standard abbreviations listed in the *International Serials Catalogue* published by the International Council of Scientific Union's Abstracting Board should be used. If the reference is to an article published without any

authorship in a periodical, the title of the article takes the place of the author in the citation, e.g. Handloom Sector of Textile Industry in India, *J Mater Sci*, 18 (1983) 1443.

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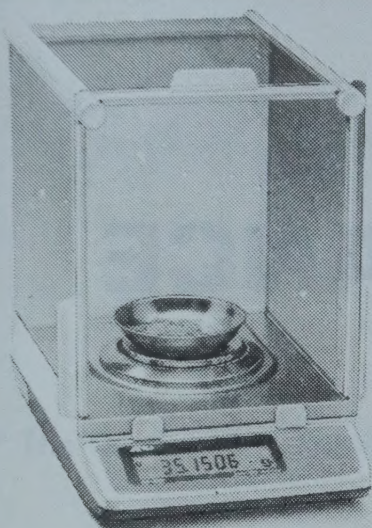
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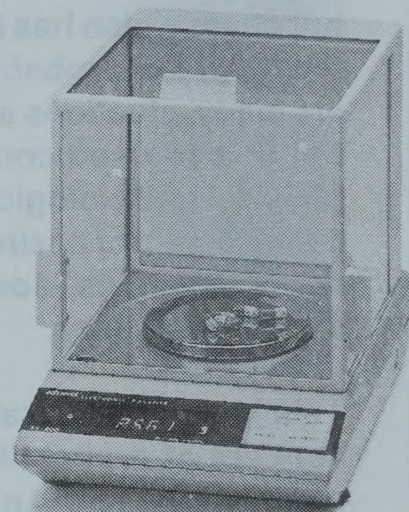


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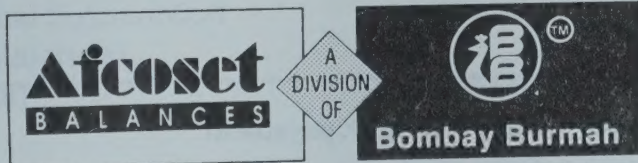
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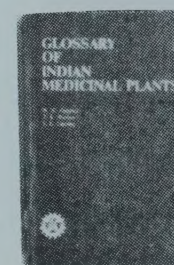
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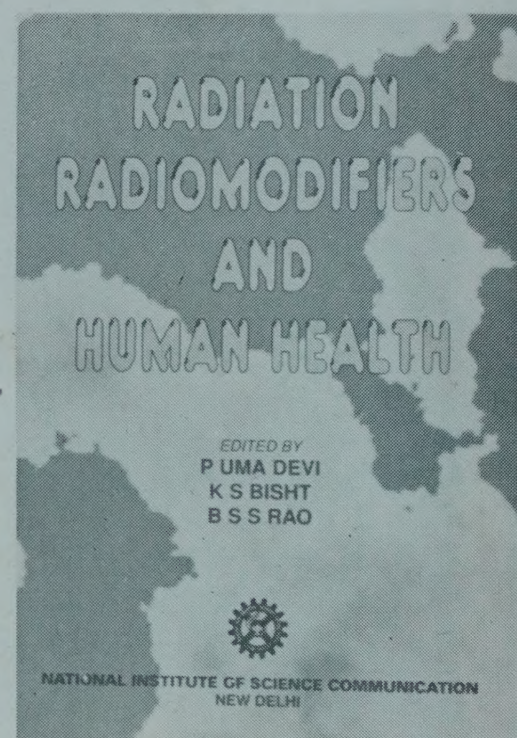
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